AFRL-HE-BR-TR-2004-0003

United States Air Force Research Laboratory

THE EFFICACY OF MODAFINIL FOR SUSTAINING ALERTNESS AND SIMULATOR FLIGHT PERFORMANCE IN F-117 PILOTS DURING 37 HOURS OF CONTINUOUS WAKEFULNESS

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January 2004

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This report has been reviewed and is approved for publication.

//SIGNED//

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REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE *(DD-MM-YYYY)*	2. REPORT TYPE	3. DATES COVERED *(From - To)*
January 2004	Interim	Jul 2003 – Jan 2004

4. TITLE AND SUBTITLE
The Efficacy of Modafinil for Sustaining Alertness and Simulator Flight Performance In F-117 Pilots During 37 Hours of Continuous Wakefulness

5a. CONTRACT NUMBER

5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER
62202F

6. AUTHOR(S)
Caldwell, John, Caldwell, Lynn, Smith, Jennifer, Alvarado, Linda, Heintz, Tara, Mylar, Jeffery, Brown, David

5d. PROJECT NUMBER
7757

5e. TASK NUMBER
P9

5f. WORK UNIT NUMBER
04

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Human Effectiveness Directorate
Biosciences and Protection Division
Fatigue Countermeasures Branch
2785 Gillingham Drive
Brooks City-Base, TX 78235-5105

8. PERFORMING ORGANIZATION REPORT NUMBER

AFRL-HE-BR-TR-2004-0003

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

10. SPONSOR/MONITOR'S ACRONYM(S)
AFRL/HE

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for public release, distribution unlimited.

13. SUPPLEMENTARY NOTES

14. ABSTRACT

The present study determined whether modafinil (100-mgs after 17, 22, and 27 hours without sleep) attenuated the effects of fatigue on fighter-pilot alertness and performance. A quasi-experimental, single-blind, counterbalanced design was used in which 5 pilots from a previous F-117 fatigue study (in which no fatigue remedy was employed) were retested with modafinil. Their data were combined with the data from 5 newly-recruited F-117 pilots who were evaluated under modafinil and then placebo. Modafinil improved vigilance and tracking performance in a divided-attention task, CNS activation, oculomotor performance, and aspects of subjective mood. Flight performance decrements were mitigated on six of eight maneuvers. Benefits were most noticeable after 24 to 32 hours of continuous wakefulness. Although modafinil did not sustain performance at pre-deprivation levels, its numerous positive effects make it a useful adjunct to the currently-approved fatigue countermeasure dextroamphetamine. However, modafinil should not be considered a replacement for this older compound. A follow-on in-flight study is recommended.

15. SUBJECT TERMS
Fatigue, Sustained Operations, Modafinil, Provigil, Aviation, Fighter Pilots, Countermeasures

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			John Caldwell
Unclass	Unclass	Unclass	Unclass	97	19b. TELEPHONE NUMBER *(include area code)* (210) 536-8251

TABLE OF CONTENTS

LIST OF FIGURES

Page

LIST OF TABLES

Page

BACKGROUND

U.S. superiority in today's battle space in part stems from our ability to maintain pressure on the enemy by making them fight around the clock. By forcing our adversaries to maintain a 24-hour-a-day operational tempo, enemy forces will suffer from severe sleepiness, leading to procedural errors, sloppy judgment, poor planning, and a general inability to react properly to rapidly changing situations. This provides a tactical advantage for the U.S. and is part of the reason that the Air Force Chief of Staff noted that persistent and sustained operations, 24 hours a day, 7 days a week, are essential to establishing and maintaining superiority in today's combat environment (Elliot, 2001). Simply forcing our enemies to perform continuously without the benefit of sufficient daily sleep is a very effective weapon in and of itself.

The Causes of Fatigue in Operational Contexts

Unfortunately, the conduct of continuous and sustained operations can pose significant hazards to our own troops if we aren't careful to properly manage fatigue among ourselves. Personnel and resource cutbacks within the U.S. Department of Defense over the past several years have resulted in force reductions of over 30 percent in the Army (Department of the Army, 1996) and in the Air Force (Congressional Research Service, 2002), while the operational tempo has increased by as much as 400 percent (Correll, 1998). Needless to say, U.S. military capabilities are increasingly strained as understaffed units strive to accomplish more work with fewer resources. Some feel that this has resulted in diminished military combat readiness (Spencer, 2000), in part, because of increased cognitive fatigue.

There is little doubt that existing manpower constraints have made it difficult to continuously staff the required work shifts with well-rested personnel around the clock. Thus, prolonged work bouts have become common, shorter-than-normal sleep periods are unavoidable, and fatigue from both of these factors threatens to impact operational readiness (Department of the Army, 1994). It is well established that sustained wakefulness and the resulting cumulative sleep debt increase the likelihood that personnel will briefly (and uncontrollably) nod off on the job, even during demanding tasks (Angus and Heslegrave, 1985). The longer personnel remain awake, the more likely these "sleep attacks" become. In addition, sleepiness takes a heavy toll on reaction time, motivation, attention, memory, endurance, and judgment (Krueger, 1991). Even in peacetime, overly tired soldiers and aviators are thought to be responsible for numerous fatigue-related incidents and accidents every year (personal communication, LtCol Thomas Luna, U.S. Air Force Safety Center, May, 2003).

The Impact of Fatigue on Military Performance

Although predictions about the exact effects of fatigue are difficult to make, most researchers agree that fatigue-related performance and alertness decrements follow a fairly reliable time course. Canadian researchers have reported that certain mental abilities decline by about 30 percent after 1 night without sleep and 60 percent after 2 nights without sleep (Angus, Pigeau, and Heslegrave, 1992). Scientists at the Walter Reed Army Institute of Research predict soldiers lose about 25 percent of their ability to perform useful mental work for every 24 hours of continuous wakefulness (Belenky et al., 1994). A recent Air Force Research Laboratory study revealed that current, active-

duty fighter pilots suffered flight-performance declines of 45 percent below normal after only 26 hours without sleep (Caldwell et al., 2003).

Fatigue Remedies for Operational Settings

It is clear that fatigue is a significant problem in sustained military operations, especially in the aviation sector where a high level of cognitive performance is essential for safety and effectiveness. However, fatigue can be managed with scientifically-validated countermeasures. Several different strategies have been proposed for this purpose.

Nonpharmacological Strategies

Emphasizing proper work/rest management is one strategy that the military has rightfully focused upon for many years. However, when the intensity of combat reaches a certain point, it can be very difficult to properly control sleep periods, and this can lead to a substantial problem with on-the-job fatigue (Cornum, 1997; Angus, Pigeau, and Heslegrave, 1992). Even during peacetime, a recent survey of U.S. Army pilots revealed that 26 percent complained of poor sleep while in the field or while traveling away from home compared to only 5 percent complaining of poor sleep at their home post (Caldwell et al., 2001). Similar difficulties are no-doubt present in the U.S. Air Force, although published documentation on this point is unavailable.

Strategic naps can help alleviate sleep-deprivation-related performance decrements in situations where naps are feasible (Dinges et al., 1988). However, scheduling naps is not a simple matter in that operational constraints can make it very difficult to ensure proper control over nap timing (placement of naps at optimal points in the sleep-deprivation period), nap duration (ensuring sufficient sleep time), and nap scheduling

(placing naps at appropriate points in the circadian cycle) (Caldwell, 2001). In addition, it can be difficult to establish a restful and isolated environment in which effective naps can take place.

Brief periods of exercise may offer some benefit in situations where full sleep periods and naps are not possible, but this strategy only temporarily reduces the impact of sleep loss (LeDuc et al., 2000; Horne and Reyner, 1995a; Angus et al., 1992). Also, there is some indication that the short-term benefits of exercise are not sufficiently robust to outweigh the alertness decrements that exercise produces later on.

Exposure to environmental stimulation such as cold air or noise is another strategy that has been tried in laboratory studies of driver fatigue. Results have shown that such measures are virtually ineffective for maintaining alertness (Horne and Reyner, 1995b).

Finally, high levels of physical fitness, while good for sustaining physical endurance, have been found to have little impact on the ability to maintain cognitive performance (Angus et al., 1992). Thus, physical fitness is not an effective fatigue countermeasure.

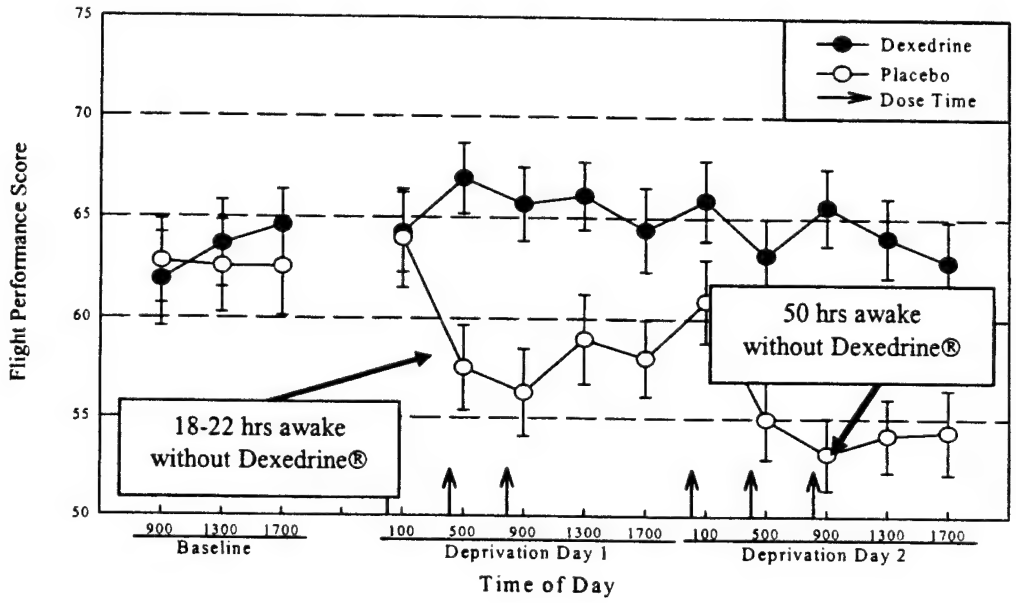
Pharmacological Strategies

Pharmacological countermeasures (alertness-enhancing compounds) may be the only reliable method for maintaining the performance of personnel, especially aviators, in sustained operations. These compounds are effective and easy to use, and their feasibility is not dependent upon environmental manipulations or scheduling modifications. This explains why drugs such as the amphetamines have been used extensively in several military conflicts (Cornum, Caldwell, and Cornum, 1997), and why the compounds caffeine and modafinil are of great interest to both the Army and the Air Force today.

Amphetamines. Amphetamines have been on the market in the U.S. since 1937 and have been widely used to treat the symptoms of medical conditions such as narcolepsy (a disorder of excessive daytime sleepiness) and hyperactivity/attention deficit disorder (Cornum, Caldwell, and Cornum, 1997). The U.S. Air Force officially authorized the use of 5-10 mg doses of amphetamine to sustain the performance of sleep-deprived pilots as early as 1961, and dextroamphetamine (marketed under the brand name Dexedrine®) continues to be authorized under Air Force policy for certain situations today. Laboratory studies have shown that single doses (20 mg) of dextroamphetamine, administered after 48 hours of continuous wakefulness, return alertness and cognitive performance to near baseline levels and maintain this recovery for 7 to 12 hours (Newhouse et al., 1989). In addition, a single 20 mg dose has been found to temporarily prevent performance decrements in subjects kept awake for approximately 34 hours, and to restore the performance of volunteers deprived of sleep for 48 hours (Pigeau et al., 1995). Multiple 10-mg doses of dextroamphetamine, administered prophylactically, are known to sustain the performance of helicopter pilots throughout 40 hours of continuous wakefulness (Caldwell et al., 1995; Caldwell, Caldwell, and Crowley, 1996; Caldwell and Caldwell, 1997), and even throughout 64 hours without sleep (Caldwell et al., 1999). Field experience with this compound has generally been positive as well (Cornum, 1997; Emonson and Vanderbeek, 1995).

There is virtually no evidence that properly-administered amphetamine increases risk-taking behaviors or overestimation of performance capabilities (Caldwell et al., 1999; Higgins et al., 1975; Baranski and Pigeau, 1997). In fact, there appears to be little reason that dextroamphetamine should not continue to be utilized as an effective fatigue

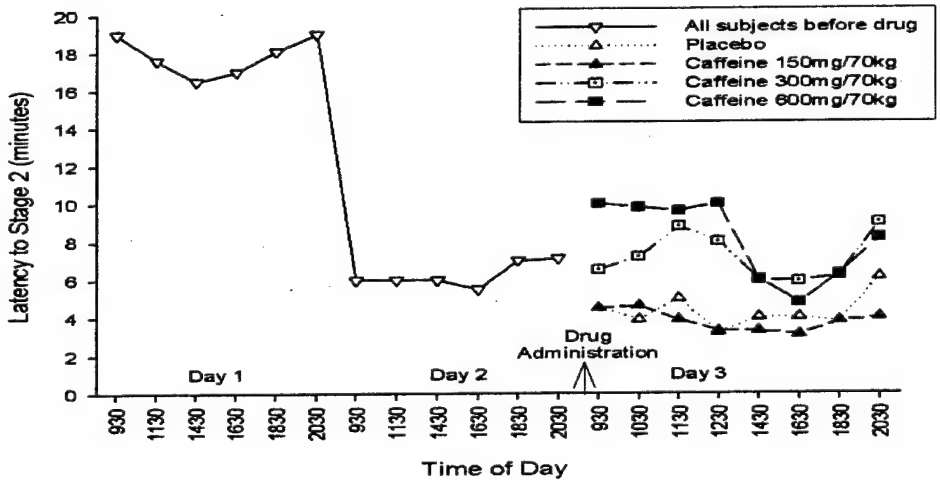
countermeasure. However, in the interest of providing flexibility to military operational personnel, it is important to evaluate potential alternatives to dextroamphetamine. Also, concerns remain about the risk of abuse that can lead to psychological or physical dependence in a subset of susceptible individuals (Akerstedt and Ficca, 1997).



Efficacy of 10-mg Doses of Dexedrine® for Sustaining Pilot Performance (from Caldwell et al., 1999).

Caffeine. Caffeine has traditionally been the first-line alternative to dextroamphetamine, primarily because it is easy to acquire and socially acceptable. Research suggests caffeine is suitable for sustaining alertness in relatively short (i.e., 37 hour) rather than long (i.e., 64 hour) periods of continuous wakefulness (Lagarde and Batejat, 1995). Caffeine appears less effective than amphetamine and more prone to produce unwanted side effects such as tremors and diuresis (Weiss and Laties, 1967), and it may be less optimal in individuals who normally consume moderate to high amounts in coffee, soft drinks, nutritional supplements, and/or food products (this has not been empirically established). However, it is known that tolerance to the sleep-disrupting

effects of caffeine (one indication of its stimulant potency) can occur in as little as 7 days in individuals given high doses (1200 mgs per day). Although most adults consume less than this amount, about 80 percent of the U.S. adult population regularly ingests a behaviorally active dose of caffeine (Griffiths and Mumford, 1995). A typical single 6-ounce serving of coffee contains 60-150 mg caffeine, tea contains 20-50 mg, chocolate contains 5-35 mg, and one Coke® contains 46 mg of caffeine (Lieberman, 1992). Thus, some degree of tolerance is inevitable, and this may mean that more than the minimum recommended dose of 200 mg caffeine would be required to noticeably improve wakefulness in sleep-deprived pilots (especially those who are chronic caffeine users). Even if this were not the case, problems related to caffeine's diuretic effects and its tendency to impair fine motor control make it of questionable value for sustaining the alertness of high-performance jet pilots. However, caffeine can significantly improve the performance of sleep-deprived people who do not normally consume high doses of this compound, and it is safe and widely available (Penetar et al., 1993).

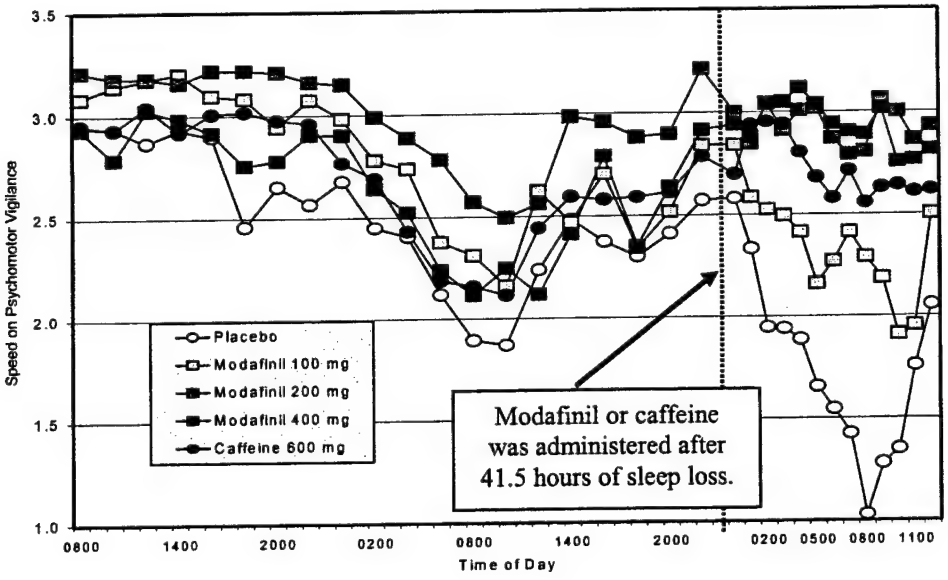


Efficacy of Three Different Doses of Caffeine for Prolonging Onset to Stage 2 Sleep (from Penetar et al., 1993).

Modafinil. Modafinil is a relatively new alertness-enhancing compound that appears efficacious for sustaining performance during prolonged periods of total sleep loss (Lagarde and Batejat, 1995). This substance became available in the United States in December of 1998 when it was approved by the Food and Drug Administration (FDA) for the treatment of excessive daytime sleepiness associated with the sleep disorder narcolepsy. Since that time, modafinil has been FDA approved for the treatment of sleepiness associated with shift work. Several studies in sleep-deprived subjects have provided evidence that modafinil is an effective fatigue countermeasure that produces few problematic side effects. For instance, Lagarde et al. (1995) and Lagarde and Batejat (1995) found that modafinil reduced the frequency of involuntary sleep lapses and maintained cognitive performance during 60 hours of continuous wakefulness. Pigeau et al. (1995) reported that modafinil (300 mg) was as effective as dextroamphetamine (20 mg) for maintaining mood, alertness, and performance throughout 64 hours of sleep deprivation. Eddy et al. (2001) reported that modafinil eliminated fatigue-related performance decrements on a vigilance task in people kept awake for 22 hours, and Wesensten et al. (2002) indicated that modafinil (200 mg and 400 mg) effectively counteracted cognitive performance decrements resulting from 41.5 hours of continuous wakefulness.

In the aviation arena, modafinil has not yet been sufficiently tested. However, the one aviator performance study conducted prior to the present evaluation (with 600 mg modafinil given in 3 divided 200 mg doses) indicated modafinil was capable of sustaining simulator flight performance at or near rested levels despite over 30 hours of

sleep loss (Caldwell et al., 2000). Unfortunately, this same study also produced evidence of side effects (nausea, vertigo, and dizziness) that may have been modafinil-related in some pilots. At this point, studies that have focused on ground-based personnel suggest that such side effects were likely an idiosyncratic reaction or that they resulted from the high dosage levels given in the earlier Caldwell et al. (2000) study. In fact, Buguet, Moroz, and Radomski (2003) and others have presented evidence that modafinil-related side effects of nausea and vomiting are clearly dose dependent. However, empirical validation of whether these side effects would occur at problematic levels with 100- or 200-mg doses, in an aviation context, was previously unavailable.



Efficacy of 100, 200, and 400 mg of Modafinil Compared to Placebo and 600 mg Caffeine (from Wesensten et al., 2002).

Modafinil is of particular interest to the Air Force (and other communities) because it lacks the abuse potential often associated with amphetamine, and it appears less likely to disrupt recovery sleep (Cephalon, 1998). In addition, modafinil does not produce the cardiovascular stimulation commonly associated with caffeine and dextroamphetamine

(Saletu et al., 1986), making it a better fatigue countermeasure for personnel who are suffering from hypertension (although this is not usually a factor in aviator populations). Despite the fact that modafinil may be better suited to counter the effects of shorter versus longer periods of sleep deprivation (Buguet, Moroz, and Radomski, 2003), its other attributes likely will make it a valuable addition to the Air Force's armament of aviation fatigue countermeasures. In fact, on 02 December 2003 modafinil was approved for use in certain Air Force bomber missions; however, approval for the use of modafinil in fighter operations was delayed pending additional research (Memorandum, Department of the Air Force Headquarters, 2003).

OBJECTIVES

Modafinil clearly has alertness-enhancing properties of interest to the military aviation community, and recent studies suggest that side effects are minimal even with 200-mg doses (as long as the 200 mg doses are spaced at 8-hour intervals). Complications from the 100 mg dose are even less likely (personal communication and unpublished data from Mr. Jeff Whitmore, Brooks City-Base, July, 2003). Thus, if it were clear that multiple, 100 mg doses of modafinil offered the required level of *alertness enhancement* and *performance sustainment* in sleep-deprived fighter pilots, modafinil could be offered as an alternative to caffeine and/or dextroamphetamine as a fatigue-countermeasure for use in "fast jet" military aviation sustained operations.

The purpose of the present investigation was to assess the utility of this (100-mg) dosage of modafinil for maintaining fighter-pilot performance in situations devoid of adequate sleep opportunities. To accomplish this objective, the effects of no-treatment/placebo versus the effects of 3 separate 100 mg doses of modafinil were

examined in active-duty F-117 pilots undergoing 37-38 hours of continuous wakefulness. The specific data of interest were:

- *objectively-measured pilot performance* during the completion of standardized flight maneuvers in a specially-instrumented flight simulator;
- *central nervous system (CNS) arousal* based on electroencephalographic (EEG) assessments of the amounts of delta, theta, and alpha activity;
- *parasympathetic/sympathetic activation* based upon measures of pupil diameter, constriction amplitude, constriction latency, and saccadic velocity;
- *self-reported measures of psychological mood states*, alertness, sleepiness, energy, and other aspects of subjective status;
- and *general cognitive status* in terms of the ability to perform simple mathematical evaluations as well as the ability to accomplish aviation-related divided-attention tasks.

METHODS

The present study employed a quasi-experimental, single-blind, counterbalanced, repeated-measures design to ascertain the efficacy of modafinil for attenuating fatigue-related degradations associated with prolonged wakefulness. Although the single-blind strategy is less optimal than the double-blind approach, the single-blind option was chosen here as a matter of necessity based on the time demands imposed on the active-duty pilot volunteers. Each of the flight squadrons from which the volunteers were recruited had only a limited number of pilots to complete the squadron's normally-scheduled missions. Therefore, the operations-group commander rightfully emphasized the importance of minimizing the research-related time demands (a secondary

requirement) on his routine squadron's primary mission requirements. One of the best ways to accomplish this objective was to include some of the data that already had been collected earlier on a subset of his F-117 pilots who had undergone sleep deprivation without the aid of a fatigue intervention, and to use these data as the no-treatment control. Since the procedures used in that previous study were identical to those employed in the present investigation, five of these individuals, who had previously received no fatigue countermeasure, were re-recruited and given modafinil in this phase of the study. Their no-treatment/treatment data were then compared to the data collected from five newly-recruited pilots, each of whom were exposed to two sleep-deprivation periods in which they received modafinil first and placebo second. This strategy resulted in only 3 days of lost time for the re-recruited pilots (half of the sample) compared to a full 5 days of lost time for the newly-recruited pilots (the other half of the sample) while still providing experimental control for the potentially confounding effects of drug-administration order.

Subjects

Ten qualified pilots (mean age of 36.6 years, ranging from 30-43 years old) who were members of the 49th Fighter Wing at Holloman Air Force Base, NM, served as participants after signing an informed consent agreement which detailed the procedures of the study. All participants were in possession of a current "up slip" (Air Force Form 1042, medical permission to engage in military flying duties) at the time of their admission, and all were current and qualified in the F-117A aircraft. The participants possessed an average of 2,730 total flight hours (ranging from 800 to 5,800 hours) and 431.5 F-117 flight hours (ranging from 140 to 890 hours). No restrictions on experience were imposed because this factor has not been shown to impact the resistance to sleep

deprivation, nor has it been shown to affect the relationship between performance capacity and electrophysiological, mood, or cognitive-performance variables in studies conducted over the past 17 years by the principal investigator of the present research. All of the participants were male because there currently are no female F-117A pilots. Prior to the study, most of the participants were reportedly on a late-daytime schedule in which they generally reported to work between 0900 and 1000 and often worked or flew until 2100 or 2200. None of the pilots were working a classic night shift (i.e., 2300-0700) or other schedule requiring duty into the predawn hours. According to actigraph data, the participants acquired an average minimum of 7 hours and 20 minutes of sleep prior to the beginning of any of the continuous wakefulness periods (further information on sleep times is provided in the Results section). None were taking any type of medication known to impact mental alertness (sedating antihistamines, sleep medications, prescription stimulants, etc.). A total of 10 pilots were evaluated because this number of participants was determined to yield sufficient statistical power based on power analyses conducted on data from an earlier study in which a similar design was employed.

Apparatus

The research protocol was conducted inside of the F-117 Weapon System Training (WST) facility at Holloman Air Force Base, NM. The flight-performance data were collected with the simulator and ancillary equipment. The remaining measures were collected with various laboratory testing devices which were set up in a co-located sound-attenuated testing room within the simulator facility. This same facility arrangement was used in the previous study on F-117 pilots which was conducted earlier this same calendar year (Caldwell et al., 2003). Between the previous study and the present investigation,

every effort was made to exactly duplicate the testing conditions since a portion of the data (no-treatment data from five participants in the earlier investigation) were included in the present data set (in which these five participants were re-recruited to undergo sleep deprivation with modafinil).

Compound to be evaluated (modafinil)

The medication was modafinil (Provigil®, Cephalon, Inc., West Chester, PA), 2-[(diphenylmethyl) sulfinyl] acetamide, in the form of 100 mg tablets. At each of the dose-administration times, the newly-recruited participants received one tablet consisting of either placebo or active compound (at midnight, 0500, and 1000). The placebo tablet was an exact replica of the active tablet so that the participants would remain blind to the drug. The re-recruited participants did not receive any type of fatigue countermeasure (or placebo tablets) during their first deprivation period (from the earlier F-117 study), but during their return to the test facility (for this second study), they all received active compound at each dose time (midnight, 0500, and 1000). Cephalon, Inc. supplied both the modafinil and placebo free of charge and without obligation of any sort whatsoever.

Multi-Attribute Test Battery (MATB)

The MATB (Comstock and Arnegard, 1992) is a computerized aviation simulation test that requires participants to perform an unstable tracking task while concurrently monitoring warning lights and dials, responding to computer-generated auditory requests to adjust radio frequencies, and managing simulated fuel flow rates (using various key presses). This test was controlled by a Micron Pentium-based computer equipped with a standard keyboard, a joystick, and a mouse. Data on tracking errors, response times,

time-outs, false alarms, and accuracy rates were calculated via the use of the MATB processing software.

Mathematical Processing

The Mathematical Processing subtest from the Automated Neuropsychological Assessment Metrics (ANAM) battery (Reeves et al., 1993) is a basic cognitive test that requires participants to solve arithmetic problems presented in the middle of the computer screen. The task involves deducing an answer to an equation such as "5 + 3 - 4 =" and then deciding if the answer is greater-than or less-than the number 5. Based on the calculation, the participant then presses one of two specified response buttons on the mouse. This test was controlled by a standard Pentium-based desktop computer equipped with a keyboard and a mouse (which was used to make the required responses to each item). Data on performance accuracy, response speed, and throughput were calculated by computer via STATVIEW™ software at the conclusion of testing.

Fitness Impairment Tester (FIT) Workplace Safety Screening Evaluation

The FIT (PMI, Inc., 1999) is a computerized fitness-for-duty test that requires participants to peer into a device in which visual stimuli (both moving and stationary) are presented. The device detects changes in pupil size (as small as 0.05 mm) and movements of the eye (as small as one degree) in response to controlled flashes of light and moving light targets. Measures of saccadic velocity, pupil diameter, pupil-contraction latency, and pupil-constriction amplitude were calculated by the FIT device and then downloaded to a Pentium-based computer for processing in a relational database.

Physiological data recording

Electroencephalographic (EEG), electro-oculographic (EOG), and electrocardiographic (EKG) recordings were collected with a Grass-Telefactor Instruments Aurora recording system (West Warwick, RI) running TWin™ collection and analysis software. For the EEG data, Grass gold-cup electrodes filled with Mevidon electrolyte gel were used (21 EEG channels were referenced to A1 and A2 during recording). For the EOG data, Grass F-E9M-60-5 11-mm Silver/Silver Chloride electrodes filled with Grass EC2 electrolyte paste were used. For the EKG data, Kendall MediTrace disposable, self-adhesive EKG electrodes were used. Data were digitized at a rate of 200 samples per second. The recording filters were set at 1.0-70 Hz for the EEG, 0.3-35 Hz for the EOG, and 1.0-35 Hz for the EKG. During all data collection (whether in the simulator or in the co-located testing room), the quality of the recordings was monitored continuously in real time in an effort to make corrections of any problems which were encountered (i.e., excessive body/eye movements or muscle artifact). Nevertheless, in the case of the data recorded in the simulator, all activity above the alpha band (more than 13 Hz) ultimately was disregarded from analysis due to the presence of muscle tension that could not be eliminated while the pilots were actively concentrating on the flight tasks.

Profile of Mood States (POMS)

Subjective evaluations of mood were made with the Profile of Mood States (POMS) (McNair, Lorr, and Droppleman, 1981). The POMS is a 65-item questionnaire which, when scored according to the specified templates, measures affect or mood on 6 scales:

1) tension-anxiety, 2) depression-dejection, 3) anger-hostility, 4) vigor-activity, 5) fatigue-inertia, and 6) confusion-bewilderment. Factor scores on each scale are analyzed.

Visual Analog Scales (VAS)

In addition to the POMS, subjective sleepiness and alertness (and other parameters) were measured via the VAS (an adaptation of the one developed by Penetar et al., 1993). This questionnaire consists of 8 lines, 100-millimeters in length, each of which is labeled at one end with the words "not at all" and at the other end with the word "extremely." Centered under each line are the test adjectives which are as follows: "alert/able to concentrate," "anxious," "energetic," "feel confident," "irritable," "jittery/nervous," "sleepy," and "talkative." The participant indicated the point on the line which corresponded to how he felt along the specified continuum at the time at which the test is taken. The score for each item consisted of the number of millimeters from the left side of the line to the location at which the participant placed his mark.

Side effects rating scale/Simulator Sickness Questionnaire (SSQ)

Once during each of the test sessions, participants were asked to complete a side-effects rating scale. This rating scale includes a total of 71 possible symptoms (including: rapid heart beats, perceptual disturbances, over stimulation, nausea, dizziness, vertigo, euphoria, tremors, headaches, dryness of mouth, upset stomach, and fatigue), each of which were rated on a scale of *none*, *slight*, *moderate*, or *severe*. Prior to administration of the side-effects scale, participants were asked to complete a computerized version of the Simulator Sickness Questionnaire (Gower and Fowlkes, 1989; Kennedy et al., 1993). This questionnaire (abbreviated as the SSQ) consists of 27 items, but only 16 of these are actually used to calculate the SSQ scores based on self-reported symptom severity

(ranging from none, to slight, to moderate, to severe). Factor scores on symptoms of nausea (gastrointestinal distress), visuomotor problems (eye-strain symptoms including headache), disorientation (vestibular disturbances), and total severity of problems (overall discomfort) are calculated.

Flight Simulator

The F-117A Weapon System Trainer (L-3 Communications/Link Simulation and Training, Binghamton, NY) was used to conduct all of the flight-performance assessments. The Weapon System Trainer (WST) is a stationary digital device that simulates the characteristics and operations of the F-117A stealth fighter aircraft that is currently in the U.S. Air Force equipment inventory. The WST provides a fully-functioning replica of the interior cockpit of the actual aircraft, including all primary and secondary flight controls, aural cues (engine sounds), and cockpit lighting (L-3 Communications, 1993). The components of the WST include the simulator itself as well as an instructor/operator station (IOS), a computer complex that includes an Alpha Server 8200 and Input/Ouput (I/O) cabinets, and the equipment necessary for the generation of out-of-the-window and IR visual scenes. The actual F-117A aircraft (simulated by this WST) is a twin-turbofan powered, low-radar, ground-attack fighter with a single-seat cockpit. The F-117A WST faithfully simulates the F-117A aircraft to the extent that training in the WST is directly transferable in terms of instrument flights, takeoffs and landings, instrument navigation, system operations, and air-to-ground attack procedures. In the present study, only the instrument-flight simulation capability was utilized.

All WST flights were set up for night illumination conditions with zero visibility and no visible lighting on the horizon. This was done to ensure that all pilots remained focused on

the flight instruments (simulated Instrument-Flight-Rules conditions) throughout the entire test period. In addition, the WST was set up to generate zero air turbulence with no wind gusts in order to prevent non-pilot-related flight-path deviations. The auto-throttle and auto-pilot modes were disengaged to force all participants to "hand fly" the simulator. Consistent with the earlier study, one of the map lights in the cockpit remained on throughout the flight profile so that the cockpit was dimly illuminated (this was done because the earlier study included eye-tracking assessments that imposed an instrumentation-based requirement for additional lighting).

Objective flight performance data were collected using the Coherent Automated Simulation Test Environment (CoASTE) tool—a set of software routines that normally provide the capability to evaluate simulator performance, display/manipulate various data from simulator data pools, and/or trace and correct problems. The CoASTE's trace utility was used to capture various parameters of flight performance data (see Table 1) at a rate of 2 Hz throughout each flight. One complete data file was generated for each simulator flight, and this file contained all of the data collected from the beginning to the end of the given simulation session. Each record in the file contained the time at which each data sample was collected, the actual data points themselves, and an identification field which consisted of the subject number, the testing day, and the testing session. The completed data files were downloaded to a Read/Write Compact Disk (CD) at the conclusion of data collection before being transferred to a standard desktop Pentium-based computer where each file was segmented into the individual maneuvers that comprised the overall flight profile. Afterwards, root mean square (RMS) errors for maneuver-relevant parameters were calculated for statistical analysis.

The measures (data points) recorded for flight-performance data analysis are shown in the table below. The individual flight maneuvers (and the measures scored for each) are later described in the Procedures section of this report.

Table 1. Measured simulator flight parameters

Number	Parameter	Range
1	Indicated altitude	0-30,000 feet
2	Indicated airspeed	30-600 KIAS
3	Indicated vertical speed	0 +/- 5,000 fpm
4	Magnetic heading	0-360 degrees
5	Pitch angle	0 +/- 90 degrees
6	Roll angle	0 +/- 90 degrees
7	Slip	0 +/- 2 balls
8	Localizer/course deviation	0 +/- 2 dots
9	Glideslope/course deviation	0 +/- 2 dots

Wrist Activity Monitors (WAM)

Wrist monitors (Ambulatory Monitoring, Inc., Ardsley, NY) were used to track sleep/activity rhythms in a relatively unobtrusive fashion. In this study, the WAMs (which are battery-powered devices about the size of a wrist watch) were used primarily to motivate subjects to follow admonishments not to sleep beyond the designated wakeup time on the morning of their test day until the time at which they reported to the Laboratory for testing (i.e., at 1800). In addition, these monitors were used to ensure the volunteers obtained sufficient sleep on the night prior to testing. Activity data were

downloaded once the participant arrived at the simulator facility for electrode application (prior to the sleep-deprivation period). The computer-generated actigraphs were visually inspected to ensure compliance with the "no nap" rule and the stated pre-study or recovery sleep times. The data from the WAMs were not further analyzed.

Procedure

In-processing

Prior to being admitted to the study, each participant's medical records were screened for current illnesses or disqualifying medications by the medical monitor or his designee at the Holloman AFB medical clinic. Afterwards, participants signed the informed consent agreement and were briefed on all of the upcoming study procedures. One of the investigators met one-on-one with each participant to address any questions or concerns that the participant may have had.

General approach

There were two groups of participants in this investigation. One group consisted of five of the F-117 pilots who were re-recruited from a previous fatigue study in which identical testing times and procedures were used (with the exception that no fatigue intervention was provided). Another group consisted of five newly recruited F-117 pilots who were tested in the present study both with a fatigue intervention (modafinil) and without a fatigue intervention (placebo). Thus, the re-recruited subjects experienced only one sleep-deprivation cycle in the present investigation (during which they received modafinil) because their previously-collected, no-treatment data from an earlier sleep-deprivation study were used as the comparison condition. The newly recruited subjects experienced two sleep-deprivation cycles separated by a period of recovery sleep in

which modafinil was administered in the first cycle and placebo was administered in the second. Although this is not the best possible experimental design, it provided a compromise between operational duty requirements (minimally conflicting with the squadron's mission schedule) and research necessities (partially controlling for subject expectancies, and fully controlling for the potential treatment/no-treatment order confound), as discussed earlier. Without this compromise, the investigation would not have been approved or conducted.

Each participant completed training/familiarity sessions prior to the beginning of the deprivation cycles, and after a suitable night of sleep, he completed five testing sessions during each of the sleep-deprivation cycles to which he was exposed. The schedules for re-recruited volunteers and newly-recruited volunteers are described below.

General schedule for re-recruited pilots

In the case of the re-recruited volunteers, only two training sessions were conducted since these volunteers had completed three training sessions and five testing sessions (using the same tests/methodologies) less than six months prior to the present investigation. This training began at approximately 1630 on the training day and ended at approximately 2030 on this same day. Refresher flights for the re-recruited subjects were conducted at 1700 and 1900. Participants were guided through the standardized flight maneuvers by members of the research staff who monitored each flight and communicated instructions to the pilot via intercom. Along with these flights, there was training on the other tests. During each training session, re-recruited participants completed two iterations of the MATB, ANAM, VAS, POMS, and FIT to refresh their knowledge and proficiency on these evaluations.

Following the afternoon/evening of re-training, and after an average of 7 hours and 40 minutes of sleep, these pilots returned to the testing facility to complete the 5 testing sessions that occurred during their single sleep-deprivation cycle. The first of these was a pre-deprivation session which began at 2100 on the day on which they reported back to the simulator facility, and the last of these was a sleep-deprivation session that ended at 2000, after 36-37 hours without sleep (the actual length of the wakefulness period was somewhat dependent on the exact wakeup time that was necessary to ensure the volunteer acquired approximately 8 hours of pre-study sleep). Modafinil was administered in 100 mg doses at midnight, 0500, and 1000.

No sleep was permitted throughout the deprivation period, and the participants were admonished not to nap from the time at which they awoke on the test morning until the time at which they reported for testing. Note that the participants had already been awake for approximately 14 hours before the first test session began. A more detailed overview of the actual sleep-deprivation testing schedule is presented after the general schedule for the newly-recruited pilots is discussed.

General schedule for the newly-recruited pilots

The newly-recruited volunteers (those who did not participate in the earlier F-117 fatigue study) completed three training sessions just like the ones that were originally provided for the participants in the previous investigation. The training began at 1330 on the training day and ended at approximately 2100 on the same day. Training flights for the newly recruited subjects were conducted at approximately 1400, 1700, and 1900. Along with these flights, there was training on the other tests. Newly-recruited participants completed six iterations of the MATB, nine ANAM tests, three VAS, three

POMS, and two FIT evaluations during training, the same as the previously-recruited participants received on their original training day. Thus, at the conclusion of the training day, newly-recruited participants had received three full training sessions on the flights, with more of the other evaluations, depending on the number estimated to be needed to reach asymptotic performance. Following the afternoon/evening of training, and after approximately 8 hours of sleep, these pilots returned to the testing facility to complete 5 testing sessions for the first of their 2 sleep-deprivation cycles. The first session was a pre-deprivation session which began at 2100 on the day on which they reported back to the simulator facility, and the last of these was a sleep-deprivation session that ended at 2000, after 36-37 hours without sleep (the actual length of the wakefulness period was somewhat dependent on the exact wakeup time that was necessary to ensure the volunteer acquired 8 hours of pre-study sleep). Modafinil was administered in 100 mg doses at midnight, 0500, and 1000 to all of the newly-recruited pilots during this first testing cycle. After release from this cycle of testing, and after approximately 9-10 hours of recovery sleep, the volunteer returned for a second sleep-deprivation cycle which began with testing at 2100 on this evening and lasted until 2000 on the evening of the next day. Placebo tablets were administered at midnight, 0500, and 1000 to all of the newly-recruited pilots during this second testing cycle despite the fact that the subjects were told the drug/placebo orders would be randomized. Sleep was not permitted on either of the test nights, and, as was the case for the re-recruited participants, these pilots were admonished not to nap between the time at which they awoke in the morning until the time at which they reported for testing. Note that a minimum of approximately 9 hours of recovery sleep was required between the two test cycles, and depending upon the

wakeup times necessary to gain this recovery sleep, the total subsequent period of continuous wakefulness fluctuated between 36 and 37 hours. Also note that the volunteers were awake for approximately 13-14 hours before the first test session began.

Schedule for both groups of pilots

Prior to reporting to the simulator building, participants were evaluated by a flight surgeon at the Holloman medical clinic at 1200 to ensure their fitness. In addition, informed consent was obtained. Next, the volunteers reported to the simulator building at designated times for their afternoon and evening training sessions as described above.

On the testing days, all of the participants were asked to wake up at 0600 (or 0700 if necessary to obtain the requisite hours of sleep). They were instructed to report to the simulator facility at 1800 for electrode application and testing preparation. Upon reporting, 25 scalp placements were marked according to the 10-20 system for electrode placement. In addition, two ECG electrodes were attached to the participant's sternum and rib cage (one each) and one EOG electrode was attached to the outer canthus of both the left and right eyes with one additional electrode attached above and below the left eye. After each placement site was cleaned with acetone, electrodes were attached to the scalp, chest, and face with collodion (EEG) or adhesive collars (ECG and EOG). Each EEG electrode was filled with electrolyte gel (through a small hole in the top of the electrode) after it was attached to the scalp. Each of the ECG and EOG electrodes was filled with electrolyte prior to attachment to the skin (these are closed electrodes which cannot be filled later). Impedances were reduced to less than 5000 Ohms at each EEG electrode prior to testing, and to less than 10,000 Ohms at each EOG electrode.

Once all of the electrodes were attached, the participant proceeded to his first EEG test which was conducted at 2100. For this evaluation, the participant was seated in the designated testing area (which was quiet and isolated) where he was connected to the EEG recording equipment and instructed to sit quietly for 2 minutes with eyes open followed by 2 minutes with eyes closed. Following EEG testing, the participant completed one POMS and one VAS. Next, he performed the MATB for 30 minutes. Afterwards, the participant completed the ANAM mathematical processing test, FIT, and another resting EEG, POMS, and VAS. Following the last VAS in each session, the participant completed the SSQ and the side-effects questionnaire.

Once the non-flight testing for the session was complete, the participant was escorted into the simulator at which time he completed an eyes-open/eyes-closed EEG while seated in the simulator (4 minutes total) prior to beginning the flight profile. Afterwards, he completed the maneuvers listed in Table 2. A staff member instructed the participant exactly when to begin each maneuver during each of the flights; however, the participants were tasked with ending the maneuvers correctly. If participants correctly maintained ideal performance parameters, all maneuvers were flown at an airspeed of 300 knots, all climbs and descents were flown at a climb/descent rate of 1000 feet per minute, and all turns were flown at a 30-degree angle of bank. Flight performance and EEG activity (as well as EOG and EKG data) were recorded continuously. Immediately following the first flight, each participant was given his drug/placebo dose (at midnight) in accordance with the general experimental plan outlined earlier. Following a rest break, which lasted for approximately 2 hours, the participant began the next non-flight test session (which

contained another series of EEG, POMS, VAS, MATB, ANAM, FIT, EEG, POMS, VAS, SSQ, and side-effects evaluations) which started at 0200 and ended at 0355.

Table 2. Flight maneuvers

Number	Detailed maneuver descriptions
1	Right 360° turn at an altitude of 11,000 feet mean sea level (MSL)
2	Straight and level on a heading of 345 degrees at 11,000 feet MSL
3	Left 360° turn at an altitude of 11,000 feet MSL
4	Straight climb from 11,000 to 13,000 feet MSL
5	Straight and level on a heading of 345 degrees at 13,000 feet MSL
6	Descending right 360° turn to an altitude of 10,000 feet MSL
7	Straight and level on a heading of 345 degrees
8	Left-climbing 540° turn to an altitude of 15,000 feet.
9	Straight and level on a heading of 165 degrees at 15,000 feet MSL
10	Right 360° turn at an altitude of 15,000 feet MSL
11	Straight and level on a heading of 165 degrees at 15,000 feet MSL
12	Left 720° turn at an altitude of 15,000 feet MSL
13	Straight descent from 15,000 to 13,000 feet MSL
14	Intercept localizer (not scored)
15	Instrument Landing System (ILS) approach to Runway 16

At 0400, the participant started the second flight, and at the conclusion of this flight, he was administered his second drug/placebo dose. After a 2-hour break, there were 3 more non-flight test sessions (0700-0955, 1200-1355, and 1700-1855) and 3 more

simulator flights (at 0900, 1400 and 1900). However, there was only one additional drug/placebo dose (after the 0900 flight). Once all of the sleep-deprivation testing was complete (following the 1900 flight), the participant's electrodes were removed, and he was debriefed and then released for the night. The testing schedule for each sleep-deprivation cycle is depicted below in Figure 1.

Time of Day	Day 1 Testing	Day 2 Testing
0200 0400 **0500**	**Wakeup**	EEG/POMS/VAS/MATB ANAM/FIT/EEG/POMS/VAS/SSQ/Side Effects FLIGHT **Drug/Placebo Dose**
0700 0900 **1000**		EEG/POMS/VAS/MATB ANAM/FIT/EEG/POMS/VAS/SSQ/Side Effects FLIGHT **Drug/Placebo Dose**
1200 1400		EEG/POMS/VAS/MATB ANAM/FIT/EEG/POMS/VAS/SSQ/Side Effects FLIGHT **----------no dose----------**
1700 1900	**Report for Testing** Electrode application	EEG/POMS/VAS/MATB ANAM/FIT/EEG/POMS/VAS/SSQ/Side Effects FLIGHT **----------no dose----------**
2100 2300 **2400**	EEG/POMS/VAS/MATB ANAM/FIT/EEG/POMS/VAS/SSQ/Side Effects FLIGHT **Drug/Placebo Dose**	***Release***

Figure 1. Schematic of each of the sleep-deprivation test cycles

To re-iterate, the test sessions, including the flights, took place at 2100-2400, 0200-0500, 0700-1000, 1200-1500, and 1700-2000; and modafinil or placebo doses were administered at 2400, 0500, and 1000. All of the re-recruited participants received modafinil at each of the three dose times during their single sleep-deprivation cycle in this study because the results from this cycle were compared to the results from their earlier no-treatment, sleep-deprivation cycle from the previous F-117 fatigue study. All of the newly-recruited participants received modafinil at each of the three dose times

during their first sleep-deprivation cycle in this study, and then received placebo at each of the three dose times during their second sleep-deprivation cycle in this study. Thus, the orders of "treatment" and "no-treatment" were completely counterbalanced (although no placebos were given in the no-treatment condition in the earlier study). The study was single blind in that none of the volunteers were aware of when/whether they were slated to receive the active compound or a placebo in this investigation.

Wrist-activity-monitor data were consulted to ensure that volunteers did not nap between their designated wake-up times and the times at which they reported for testing. To ensure proper wake-up times in the pilots who completed a second deprivation cycle after a night of recovery sleep (the newly-recruited volunteers), a member of the staff provided a wake-up call at the predetermined time on the morning of their second continuous wakefulness period. While in the simulator testing facility, meals and/or snacks were furnished *ad lib*. Each participant was continuously monitored from the time he reported to the test facility until his departure to ensure that prohibited or involuntary sleep episodes did not occur during the deprivation testing.

At the conclusion of the deprivation periods, participants were driven home by a staff member or a family member. Participants were cautioned that they should not drive, operate complex machinery, or engage in other potentially dangerous tasks until they had obtained at least one full night of normal sleep. Furthermore, participants were restricted to duties not including flying (DNIF) for a minimum of 48 hours following any period of sleep deprivation.

DATA ANALYSIS

As noted earlier, there were two iterations of EEG, POMS, and VAS testing during each non-flight test session. In this report, only the tests that were performed closest to the simulator flights were analyzed. Since there was a time interval of several weeks between the initial testing of half of the participants (from the earlier fatigue study) and the present re-testing of these volunteers, it was felt necessary to correct for any potentially-confounding intervening factors that may have differentially affected performance on the two occasions. In addition, since the other half of the subjects only had one day and night to recover between the two sleep-deprivation periods, it seemed conservative to correct for any possibly-confounding effects of incomplete recovery between the two test cycles. The technique chosen to achieve these corrections across all of the deprivation cycles was to consider the first testing session in each cycle (the 2100-2400 session) as a "baseline," and to adjust the subsequent performance, physiological, and self-report data according to what was observed during this baseline. Therefore, all of the data for the remaining four deprivation test sessions (0200-0500, 0700-1000, 1200-1500, and 1700-2000) were expressed as percent change from this initial baseline, and these were the data that were analyzed.[1]

Missing data were handled via BMDPAM which substituted the cell means for any missing observations (with the exception of the flight-EEG data, there was never more than 5 percent of data loss due to equipment failures or any other problems). Afterwards,

[1] As a check to ensure that there were no confounding effects attributable to whether subjects belonged to the first group (re-recruited participants) versus the second group (newly-recruited participants), an additional analysis was performed on all of the flight data in which a grouping factor was included (first versus second group). Since the results indicated that the grouping factor did not interact with the Condition factor, the Time factor, or the Condition-by-Time effect, it was dropped from subsequent ANOVAs.

the data (non-flight and flight) were initially analyzed with BMDP4V, Repeated Measures Analysis of Variance (ANOVA). Huyhn-Feldt adjusted degrees of freedom were used to compensate for any observed violations of the compound symmetry assumption that is critical for accuracy in repeated-measures ANOVA (note that this correction results in fractional degrees-of-freedom values). Follow-up (post-hoc) tests most frequently consisted of analysis of simple effects and/or regression evaluations for the presence of linear, quadratic, and cubic trends (also calculated with BMDP4V). Trend analysis was used in place of pairwise contrasts in an effort to minimize alpha inflation (for the four baseline-adjusted test times, only three trend analyses were necessary as opposed to the six posthoc tests that would have been necessary for all possible pairwise comparisons).

For most of the data, two-way ANOVAs were used since there were two drug conditions and four baseline-corrected iterations of testing. However, both the EEG data and the flight-performance data required analysis with a three-way ANOVA because there were three design factors of interest in these data sets. For the resting EEGs, data were collected under two treatment conditions, at four testing times, and under both eyes-open and eyes-closed conditions. For the simulator EEGs (collected while the participant was flying the maneuvers), data were collected during the preflight eyes-open condition, the preflight eyes-closed condition, and during each of the maneuvers under both treatment conditions at each of the deprivation testing times (for reasons which will be explained later, these in-flight EEGs actually were not analyzed). With the flight-performance data, there were two treatment conditions, four baseline-corrected testing iterations, and eight maneuver types (combined right 360° turns, combined straight-and-

levels, left 360° turn, straight climb, straight descent, left-climbing turn, left 720° turn, and right descending turn).[2] These maneuver types were analyzed together in a condition-by-maneuver-by-time ANOVA after they were analyzed separately in a series of two-way ANOVAs. To combine the two right turns with one another, the performance scores were simply averaged prior to analysis. To combine the five straight-and-levels, the same approach was used.

The flight performance data collected from the 0400, 0900, 1400, and 1900 flights were initially converted into RMS errors prior to their conversion into percentage-of-change-from-baseline (i.e., change from the 2300-hour test flight). The RMS errors were based upon different parameters from the various maneuvers because, for instance, it would make little sense to evaluate heading deviations during turns since the heading in a turn necessarily must change in order to accomplish the maneuver. The specific parameters that were evaluated for each of the maneuvers are depicted in table 3. The RMS errors were calculated by subtracting the observed moment-to-moment parameter values (sampled at a rate of 2 Hz) from the target value for that particular parameter.[3] This deviation score was squared, then summed across the entire maneuver. The result was divided by the total number of samples collected during the maneuver, and then, the square root of this result was obtained (the formula for calculating RMS errors is the same as the one used to calculate standard deviations except that deviations from the target value rather than deviations from the mean are of interest).

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[2] The ILS approach will not be analyzed at this point due to technical issues which have not yet been resolved. Specifically, the distance from the runway was inadvertently not recorded in the flight data set.

[3] To minimize the chances of RMS errors becoming inflated due to improper maneuver set up rather than to increased control variability, all participants were required to be within 2 degrees of the target heading, 5 degrees of the target airspeed, and 20 feet of the target altitude before each maneuver was started.

All data (flight and non-flight) were converted into scores that represented the "percentage change from baseline" prior to analysis. This was accomplished in a series of steps. First, for each iteration of each test, the score that was derived from this same test during the first session in the deprivation cycle (baseline) was subtracted from the score that was derived during each of the subsequent deprivation-testing iterations (for the flight data, the score was subtracted from the baseline since the flight data consisted of RMS errors, and we wished to show reductions in accuracy rather than increases in errors). Next, the results of these calculations were divided by the baseline score. Finally, the outcomes were each multiplied by 100. Thus, the formula used for all of the non-flight tests (except the EEGs) was as follows:

Percent Change = ((Score – Baseline)/Baseline) x 100.00.

Whereas the percent-change-from-baseline score for the RMS errors stemming from the simulator flight data was:

Percent Change = ((Baseline - Score)/Baseline) x 100.00.

For example, the POMS fatigue score earned by a participant during his 0330 POMS at the second session of the deprivation period was subtracted from the POMS fatigue score he earned in the first session at 2230. The result was then divided by the baseline score (collected at 2230) and multiplied by 100. The same series of calculations was performed for the POMS fatigue scores earned at each subsequent deprivation session (0830, 1330, and 1830). In this way, it was possible to calculate the percentage increase (or decrease) in self-rated fatigue throughout the deprivation period, adjusting for the fact that a participant may have reported to one of his deprivation periods already feeling

more (or less) fatigued than he had been when reporting to his other deprivation period. This same basic procedure was used on all of the other data as well.

Table 3. Parameters evaluated in each of the flight maneuvers.

Maneuver	Altitude	Airspeed	Vertical Velocity	Heading	Roll
Right 360° Turn No. 1	x	x			x
Straight-and-Level No. 1	x	x		x	
Left 360° Turn	x	x			x
Climb		x	x	x	
Straight-and-Level No. 2	x	x		x	
Right Descending Turn		x	x		x
Straight-and-Level No. 3	x	x		x	
Left Climbing Turn		x	x		x
Straight-and-Level No. 4	x	x		x	
Right 360° Turn No. 2	x	x			x
Straight-and-Level No. 5	x	x		x	
Left 720° Turn	x	x			x
Descent		x	x	x	

The strategy of calculating and analyzing percent-change scores not only provided an appropriate method for examining the effects of fatigue on all of the individual laboratory tests conducted in this research, it also offered an avenue for calculating composite flight scores for each of the flight maneuvers. This is because normally it would not be possible to combine measures of different flight parameters within the same maneuver --

such as headings, altitudes, and airspeeds -- due to the fact that each of these are based on different scales (i.e., headings are expressed in degrees, altitudes are expressed in feet, and airspeeds are expressed in knots). However, by converting each of the measured flight parameters to a *percentage of change from baseline*, (using the first flight in the test cycle as the baseline) all of the individual parameter scores (headings, altitudes, airspeeds, etc.) – now expressed as percentages – could be averaged together to represent overall maneuver performance during each of the deprivation flights. Had this not been the case, it would have been necessary to individually analyze each relevant parameter from each of the flight maneuvers, and this would have created a problem with alpha-rate inflation due to the large number of statistical comparisons required. In fact, with 3 relevant measures per maneuver type, and with the relevant measures changing as a function of the particular requirements of each maneuver, a minimum of 24 separate ANOVAs would have been necessary as opposed to the 8 ANOVAs which permitted analysis of each maneuver separately, plus a single additional ANOVA which enabled the evaluation of the composite percent-change scores from all maneuvers combined.

The method for analyzing the flight data was as follows: once all RMS errors had been calculated and all flights for a particular subject were complete, change-from-baseline scores were calculated for each of three relevant parameters (i.e., heading, altitude, airspeed, etc.) for each maneuver. Finally, the three percent-change-scores for each maneuver were averaged together to yield one composite change-from-baseline score for each maneuver within each of the deprivation flights. For the combined maneuver analysis, these data were analyzed in a three-way ANOVA as explained earlier.

In addition, each maneuver was analyzed separately to examine the consistency of effects across all eight maneuver types.

EEG data were classified into the 4 standard activity bands of delta (1.5-3.0 Hz), theta (3.0-8.0 Hz), alpha (8.0-13.0 Hz), and beta (13.0-20 Hz) by calculating the power spectrum (using a Hamming window) on 3 epochs of 2.5 seconds each within each EEG segment of interest. This procedure was used for both the resting EEG collected in the co-located testing room (prior to each flight) and the resting EEG collected in the simulator prior to the initiation of the flight maneuvers. The same was done for the EEG segments that were collected during each subject's performance of each of the flight maneuvers. Each band was analyzed in a three-way, repeated measures analysis of variance (ANOVA) in which the factors are as follows: 1) for the laboratory data (collected in the co-located testing room), the factors were treatment condition (treatment and no-treatment), baseline-corrected time (0320, 0820, 1320, 1820), and eyes (eyes open, eyes closed); 2) for the in-flight data, the factors were treatment condition (treatment and no-treatment), baseline-corrected time (0400, 0900, 1400, and 1900), and section (resting eyes-open in the simulator, resting eyes-closed in the simulator, EEG collected during SL-3, and EEG collected during SL-5). Note that in the present report, only the resting EEG data collected immediately prior to each flight have been examined. The remaining resting EEG data will be the subject of a future report.

The EKG and EOG data collected during the flight testing in this investigation have been stored on disk and transferred to Dr. Glenn Wilson at Wright Patterson Air Force Base, OH, where they first will be pre-processed (converted into blinks per minute, beats

per minute, and heart-rate variability) and then subjected to three-way ANOVAs for condition, time, and maneuver. A report on the outcome of this analysis is forthcoming.

The percent-change scores from each of the items on the VAS (i.e., sleepiness, alertness, energy, etc.) and each of the factor scores on the POMS (i.e., fatigue, confusion, vigor, etc.) were analyzed with a series of two-way ANOVAs across treatment conditions and baseline-corrected deprivation testing times (0330, 0830, 1330, and 1830). Only the self-report/mood data that were collected closest to the flights were examined in this report. Each set of scores from both the VAS and the POMS were analyzed separately.

The percent-change scores on the reaction times, time outs, hits, misses, and tracking errors from the four subtests of the MATB (communications, system monitoring, resource management, and tracking) also were analyzed separately with a series of two-way ANOVAs for treatment condition and baseline-corrected testing time (0230, 0730, 1230, and 1730).

The percent-change scores from the FIT Workplace Safety Screener (pupil diameter, constriction latency, constriction amplitude, and saccadic velocity) were each subjected to a two-way ANOVA for treatment condition and baseline-corrected testing time (0315, 0815, 1315, and 1815).

The percent-change factor scores from the SSQ (nausea, visuomotor problems, disorientation, and total severity of problems) were analyzed with a two-way ANOVA for treatment condition and testing time. This was done only on the five newly-recruited subjects since no data were available on this particular instrument for the first deprivation cycle of the re-recruited participants (who had participated in the earlier fatigue study).

The most relevant indicators from the side-effects questionnaire (those concerned with 1) a *drugged feeling*, 2) *light headedness*, 3) *loss of coordination*, 4) *nausea*, 5) *vertigo*, 6) *confusion*, and 7) *headache*) were summarized for each treatment condition (frequency counts were calculated with Excel™). Only the side-effects ratings for the newly-recruited participants were evaluated since the re-recruited participants were not administered this evaluation during their earlier fatigue study (in which no intervention was provided).

RESULTS

The cognitive data (MATB and ANAM), physiological data (EEG and FIT oculomotor), subjective mood/alertness data (POMS and VAS), objective flight performance data, and subjective simulator-sickness data (SSQ) were assessed with independent repeated-measures ANOVAs. All significant effects were then further analyzed with analysis of simple effects and/or with BMDP contrasts to pinpoint the exact nature of the observed differences. The contrast analyses (conducted in the event of test-session main effects or session-related interactions) examined the data for the presence of linear, quadratic, and cubic trends.

When presenting the results of these analyses, the two levels of the condition factor will be described as "modafinil" and "placebo." The "placebo" terminology will be used even though in actuality, placebo tablets were not given to the re-recruited participants during their initial no-treatment sleep-deprivation test cycle in the earlier fatigue study. It is simply more straightforward to use the term "placebo" as opposed to "placebo/no-treatment."

Sleep-estimate data and side-effects data were not statistically analyzed. However, they are described in sufficient detail to aid in the interpretation of other results.

General Participant Characteristics

As noted earlier, one group of participants was given no treatment (no fatigue intervention) during the first sleep-deprivation cycle and modafinil during the second sleep-deprivation cycle. A second group was given the opposite treatment order, with modafinil first and no treatment (placebo) second. ANOVAs on the general characteristics of these two groups indicated that they were essentially comparable in that there were no statistically-significant differences in their ages, their total flight hours, or their F-117 flight hours (see table 4). Thus, any observed effects in the subsequent analyses are unlikely to have been contaminated by inequitable group characteristics.

Table 4. Age and flight experience data for the two groups

Participant Group	Age	Total Flight Experience	F-117 Flight Experience
Re-recruited pilots	35.2	2,660 h	411 h
Newly-recruited pilots	38.0	2,800 h	452 h

Sleep Estimates

To determine whether the two groups of pilots (re-recruited versus newly-recruited participants) acquired sufficient sleep prior to reporting for their sleep-deprivation testing, the actigraph-based sleep estimates, bed times, and wake times were examined. This examination indicated that overall, the average duration of the periods of continuous wakefulness to which the pilots were exposed was about 37 hours (the average wake-up time was 0651 prior to the first period and 0729 prior to the second period). On average,

the participants gained approximately 7.5 hours of sleep prior to their first continuous-wakefulness episode and approximately 8.5 hours of sleep prior to their second continuous-wakefulness episode. As can be seen in Table 5, the difference between the two sleep periods was attributable to the fact that newly-recruited participants followed instructions to "try to acquire 10 hours of sleep between the first and second deprivation period" in an effort to minimize concerns over incomplete recovery from their first 37-hour episode of continuous wakefulness. Note that this was not a concern for the re-recruited volunteers because there was a time interval of several weeks between their first and second sleep-deprivation cycles. They were simply told to get 8 full hours of sleep.

Table 5. Actigraph-based estimates of sleep times

Participant Group and Sleep Episode	Sleep Start (Range)	Sleep End (Range)	Sleep Duration (Range)
Re-recruited pilots	2328	0648	7h 20m
Prior to first continuous wakefulness	(2250-0030)	(0600-0700)	(6h30m-8h0m)
Re-recruited pilots	2325	0702	7h 41m
Prior to second continuous wakefulness	(2230-0005)	(0650-0720)	(7h0m-8h30m)
Newly-recruited pilots	2302	0654	7h 56m
Prior to first continuous wakefulness	(2245-2315)	(0645-0700)	(7h45m-8h15m)
Newly-recruited pilots	2227	0756	9h 41 m
Prior to second continuous wakefulness	(2200-2320)	(0740-0800)	(8h40m-10h30m)

Multi-Attribute Task Battery

The MATB consists of four concurrently-administered subtests that were evaluated during each test session. The subtests were: communications, systems monitoring, fuel

monitoring, and unstable tracking. As described below, a variety of performance indicators were collected on each of the subtests, and prior to analysis, these data were transformed into percent-change-from-baseline scores using the data from the 2130 test (at the onset of the sleep-deprivation period) as the baseline. Following the percent-change transformation, each MATB measure was analyzed in a separate two-way ANOVA to determine whether there were differences between the two test conditions (modafinil, placebo), across the various sleep-deprivation testing times (0230, 0730, 1230, and 1730), or whether there were interactions between conditions and test sessions.

Communications

In the communications task, participants responded to simulated radio calls by dialing in a designated "radio frequency." The reaction time (RT), standard deviation of reaction times (SDRT), accuracy, and time-out (TO) errors were analyzed. Of these outcome measures, a marginally-significant condition main effect was found on SDRT ($F(1,9)=4.79$, $p=.0563$), and a significant condition main effect was found on TO errors ($F(1,9)=9.57$, $p=.0129$). In the case of SDRT, the overall baseline-corrected percentages actually indicated less variability, or better performance, under placebo than under modafinil (the means were 3.85 and 16.35, respectively). In the case of the TO errors, the results were more in line with expectations in that errors were lower (performance was better) under modafinil than under placebo (the means for the two conditions were 49.17 and 194.17, respectively). Further examination of the SDRT data indicated that performance across all test sessions was similar under modafinil. However, under placebo, performance was much different at the 0230 session than elsewhere (SDRT was almost 12 percent better compared to baseline). Primarily due to this single session, the

overall percentage change in performance under placebo (with sessions collapsed) appeared better than under modafinil. These results are considered spurious since it is clear that the percent-change SDRT results are the opposite of the untransformed SDRT data as well as the other MATB findings. Therefore, the baseline-corrected SDRT results will, at least for the present, be discarded.

The TO-error results are, however, considered valid since the baseline-corrected results were consistent with the untransformed TO errors in showing that participants were more vigilant on the communications subtask under modafinil than under placebo. In addition to the findings with regard to treatment condition, there was a time main effect on TO errors ($F(2.41,21.66)=3.79$, $p=.0322$) which subsequent analyses indicated was marginally attributable to a quadratic trend in the data ($p=.0819$). Overall, TO errors increased very little from baseline to 0230, but at all of the later testing times, TO errors were consistently elevated. Figure 2 shows the general impact of both condition and testing time on TO errors.

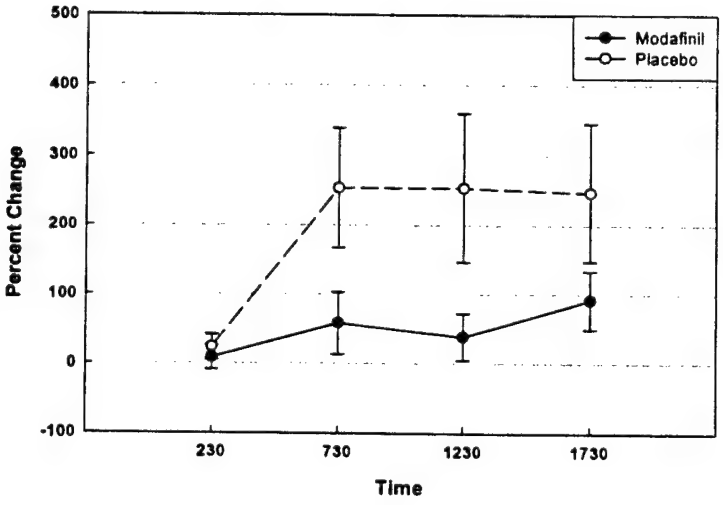

Figure 2. The effects of treatment condition and testing times on TO errors during the MATB communications task.

Systems monitoring

In the monitoring task, participants monitored various warning lights and dials, and their RT for each response, the SDRT, and the TO errors (missed signals) were assessed during each iteration of the task. The two-way ANOVA indicated that neither of these measures was affected by the modafinil/placebo treatment conditions nor by the combination of treatment condition and testing time. However, there was an overall time main effect on the baseline-corrected SDRTs ($F(3,27)=3.50$, $p=.0290$) and the baseline-corrected RTs ($F(2.97,26.74)=5.24$, $p=.0058$). In both cases, further analysis indicated the presence of significant ($p<.05$) quadratic trends which resulted from pronounced and sustained increases in response variability and RT errors only after the 0230 testing time. As shown in figure 3, this degraded performance continued until the end of the sleep-deprivation period.

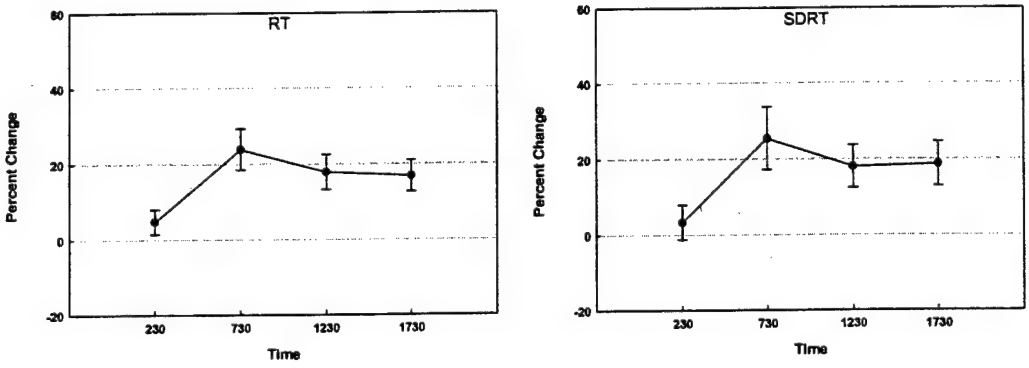

Figure 3. The effects of sleep deprivation (with treatment condition collapsed) on RT (left) and SDRT (right) during the MATB systems-monitoring task.

Fuel monitoring

In addition to monitoring lights and dials, participants were required to maintain the fuel levels in simulated fuel tanks at 2500 pounds. The two-way ANOVA on the absolute deviation from this target value indicated that there was no condition main effect

and no condition-by-time interaction. However, there was a significant time main effect ($F(2.74, 24.66)=3.83$, $p=.0249$). Trend analysis revealed that this was due to a quadratic pattern that resulted from a particularly sharp increase in fuel-tank deviations after the 0230 testing time ($p<.05$). Performance was much worse at 0730 than at 0230, as well as at 1230 or 1730 (see figure 4).

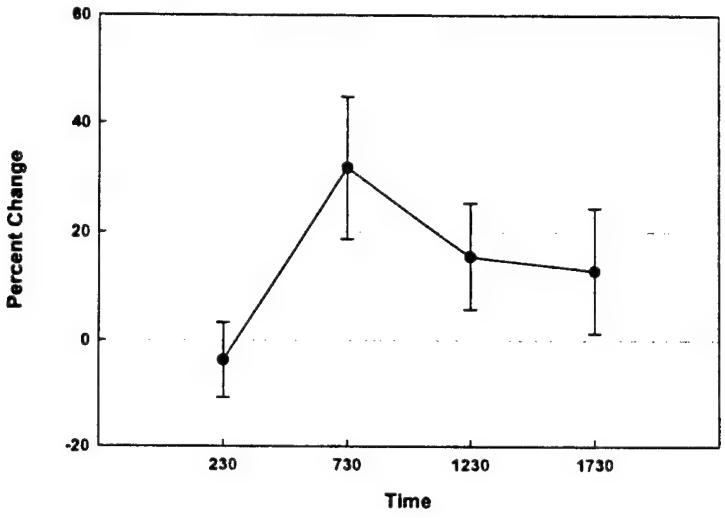

Figure 4. The effects of sleep deprivation (with treatment condition collapsed) on the deviations of fuel levels in tanks A and B during the MATB fuel-monitoring task.

Unstable tracking

The tracking task required participants to maintain an unstable target at a point in the middle of the tracking window while performing the other subtasks mentioned above. Analysis of the tracking errors revealed a condition main effect ($F(1,9)=6.87$, $p=.0277$), a time main effect ($F(2.07,18.67)=11.17$, $p=.0006$), and a condition-by-time interaction ($F(2.87, 25.79)=3.30$, $p=.0381$). Analysis of simple effects indicated that there was no difference between modafinil and placebo at 0230, but that performance under modafinil was consistently better than performance under placebo at 0730, 1230, and 1730 ($p<.05$). The overall condition main effect was consistent in that the average percent-change-

from-baseline tracking error under modafinil was 39.2 whereas the percent-change error under placebo was 84.9. The overall time main effect was due to linear, quadratic, and cubic trends ($p<.05$) that resulted from a general fatigue-related degradation in performance that was particularly pronounced at 0730 before it improved slightly from 0730 until the end of the deprivation period. All of these condition and time effects are shown in figure 5.

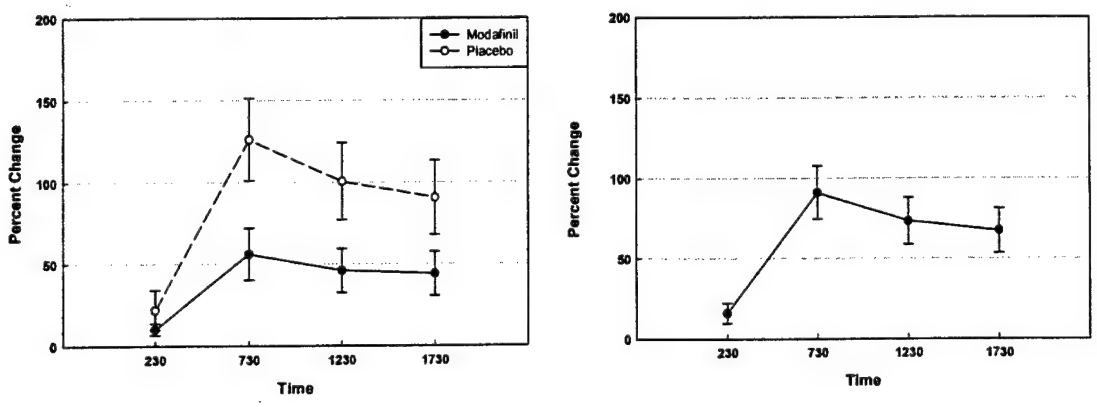

Figure 5. The combined effects of treatment condition and testing time (left) and the overall effect of time on MATB tracking (right).

Mathematical processing

The mathematical processing task from the ANAM battery was analyzed in terms of RT for correct responses, SDRT for correct responses, overall accuracy, and number of correct responses per minute (throughput). Prior to analysis, these data were transformed into percent-change-from-baseline scores, using the data from the 2205 test (at the beginning of the deprivation period) as the baseline. Following the percent-change transformation, each measure was analyzed in a separate two-way ANOVA to determine whether there were differences as a function of treatment condition and/or the various sleep-deprivation testing times (0305, 0805, 1305, and 1805).

Reaction time for correct responses

The two-way ANOVA on the RT data revealed no effects attributable to condition or testing time. Also, there was not an interaction between these two factors.

Standard deviation of RT for correct responses

The analysis of the RT variability data for correct responses indicated there was not a significant condition-by-time interaction. Also, the main effects for condition and time were not significant.

Accuracy

The accuracy data indicated there were no differences between the two treatment conditions or the four testing times. Also, condition and time did not interact.

Throughput

The number of correct responses per minute (a combined speed/accuracy measure) was not affected differentially by treatment condition or testing time. There also were no interactive effects attributable to these factors.

Oculomotor (FIT) data

There were four oculomotor measures collected during each of the five equally-spaced test sessions. The measures were pupil diameter, pupil constriction amplitude, pupil constriction latency, and saccadic velocity. Prior to analysis, these data were transformed into percent-change-from-baseline scores using data from 2215, at the outset of the sleep deprivation periods (one for modafinil and one for placebo). Following the data transformations, each oculomotor measure was analyzed in a separate two-way ANOVA to determine whether there were differences due to condition (modafinil, placebo) and/or the various sleep-deprivation testing times (0315, 0815, 1315, and 1815).

Pupil diameter

Measurements of the participants' initial pupil diameters indicated a significant condition-by-time interaction ($F(2.68,24.09)=4.54$, $p=.0140$) and a significant time main effect ($F(1.41,12.67)=4.41$, $p=.0458$). Although there was a tendency toward a condition main effect, it did not attain statistical significance ($p=.07$). The interaction was due to significantly smaller pupil size under placebo relative to modafinil at both the 1315 and 1815 ($p<.05$) test sessions, whereas there were no significant differences between the two conditions at 0315 or 0815. This effect is depicted in figure 6 (left). The time main effect was attributable to both linear and quadratic trends. With the two treatment conditions collapsed, pupil size was only slightly smaller during the 0315 test than pupil size at baseline, whereas it was much smaller at 0815 and 1315. Afterward, at 1815, pupil diameter returned to a size that was slightly larger than the size that was measured at the pre-deprivation baseline (see figure 6, right).

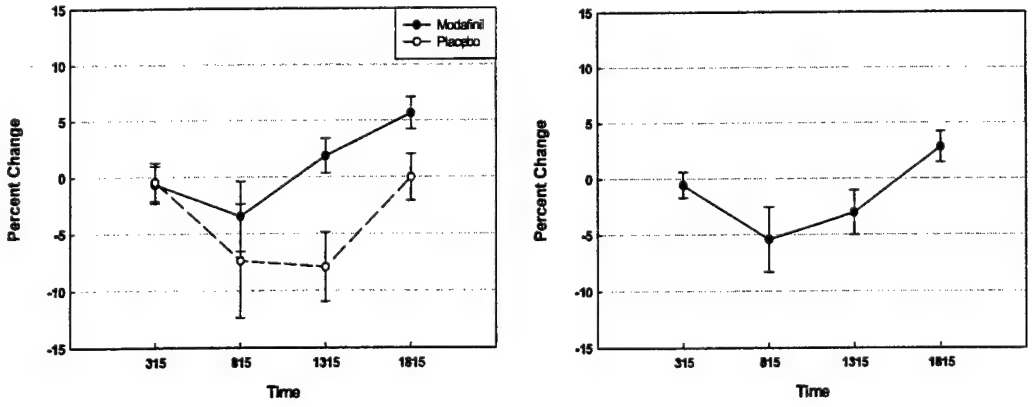

Figure 6. The combined impact of treatment condition and testing time (left) and the overall effect of testing time (right) on FIT pupil diameter.

Pupil constriction amplitude

The degree to which the participants' pupils constricted in response to brief flashes of light was unaffected by the treatment conditions or the testing times used in this study. No changes were observed as a function of either design factor.

Pupil constriction latency

The amount of time from the onset of light flashes until pupil constriction was not affected by whether modafinil or placebo was administered. However, there was a significant time main effect ($F(3,27)=7.47$, $p=.0009$) which was due to the presence of linear, quadratic, and cubic trends ($p<.05$). The mean constriction latencies, although initially longer than those observed at baseline, became progressively shorter with increased sleep deprivation. There was an especially-noticeable decrease from 0815 to 1315. Then, although the constriction latency at 1815 remained shorter than the ones at 0315 or 0815, the latency at 1815 was longer than the latency at 1315. This overall time effect is shown in figure 7.

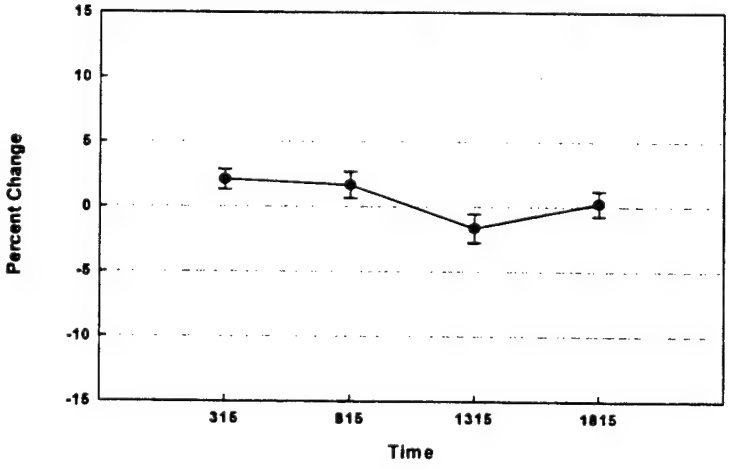

Figure 7. The overall effect of sleep deprivation (testing time) on FIT pupil constriction latency.

Saccadic velocity

The speed of saccades was affected by the additive influence of both condition and time ($F(3,27)=3.50$, $p=.0290$) as well as by the singular impact of condition ($F(1,9)=9.05$, $p=.0147$). Analysis of simple effects indicated that the interaction was due to the presence of differences between the modafinil and placebo conditions at 0310, 0810, and 1310, but not at 1810. At the first three testing times under modafinil, saccadic velocity was maintained essentially at baseline levels; however, at these same testing times under placebo, saccadic velocity was substantially below baseline levels ($p<.05$). At 1810, the speed of saccades under both modafinil and placebo converged to nearly identical levels. These interactive effects are graphically depicted in figure 8. The condition main effect generally supported what was observed in the condition-by-time interaction in that saccadic velocity under modafinil changed only slightly throughout the deprivation period whereas saccadic velocity under placebo dropped significantly at least until the end of the day.

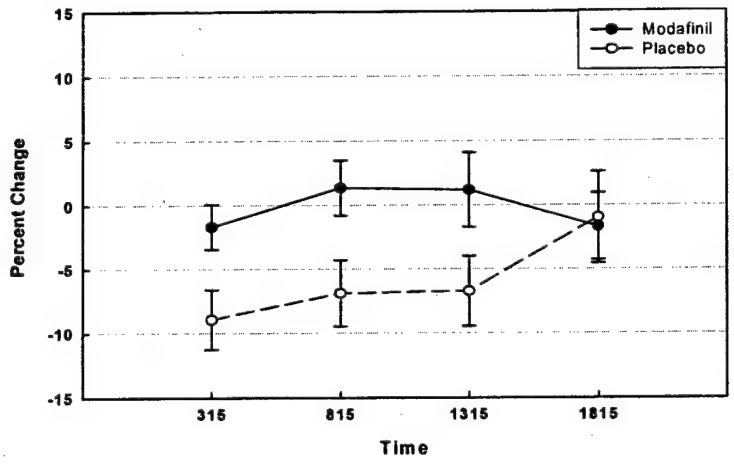

Figure 8. The combined impact of treatment condition and testing time on FIT saccadic velocity.

Resting EEG data

Resting EEG data were collected under eyes-open and eyes-closed conditions (2 minutes of each) at each of the deprivation sessions. From each of the 2-minute segments, a minimum of three 2.5-second epochs was selected, and these were used to calculate the absolute power of delta, theta, and alpha activity. For the present report, only the data from the midline electrodes (Cz, Pz, and Oz) are presented.

All of the EEG data were transformed in the same manner as the other measures. They were expressed as a percentage of change from the first EEG tests which were conducted at the outset of the deprivation cycles (i.e., change from the 2225 sessions). Each of the activity bands were analyzed separately in independent three-way ANOVAs for condition (modafinil, placebo), time (0320, 0820, 1320, and 1820), and eyes (open and closed).

Delta activity

The analysis of the percent-change-from-baseline absolute power within the 1.5-3.5 Hz range indicated condition-by-eyes interactions at Cz ($F(1,9)=17.95$, $p=.0022$) and Pz ($F(1,9)=20.22$, $p=.0015$). In both cases, analysis of simple effects revealed there was a significantly greater increase in delta activity under placebo than under modafinil at eyes closed, but not at eyes open ($p<.05$). These results are graphically depicted in figure 9.

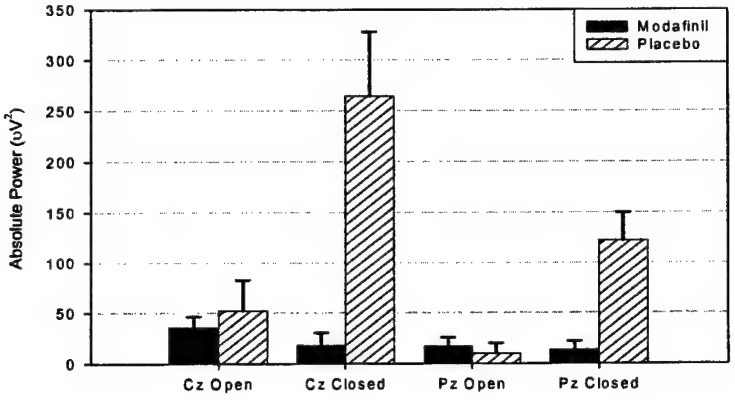

Figure 9. The interactive effects of treatment condition and eye closure on resting EEG delta activity at Cz and Pz.

In addition to these two interactions, there were significant main effects for condition at Pz ($F(1,9)=6.09$, $p=.0357$) and Oz ($F(1,9)=6.85$, $p=.0279$) as well as a marginally-significant condition effect at Cz ($F(1,9)=4.81$, $p=.0560$). As shown in figure 10, all of these resulted from a much larger increase in delta (relative to baseline) under placebo than under modafinil.

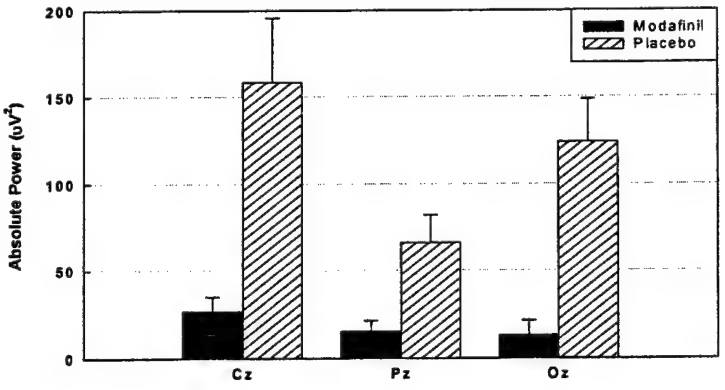

Figure 10. The overall condition main effects (modafinil versus placebo) on resting EEG delta activity at Cz, Pz, and Oz.

There were time main effects at Pz ($F(12.27)=20.22$, $p=.0290$) and Oz ($F(2.70,24.30)=3.58$, $p=.0320$) as well. Subsequent analyses indicated that at Pz, there were both linear and quadratic trends that resulted from a general increase in delta from

the first testing time throughout the later testing times as well as an especially-noticeable increase between the 0320 test and the 0820 test. At Oz, only the linear trend was significant ($p<.05$), although the overall pattern of time-related effects was similar to what was observed at Pz (see figure 11).

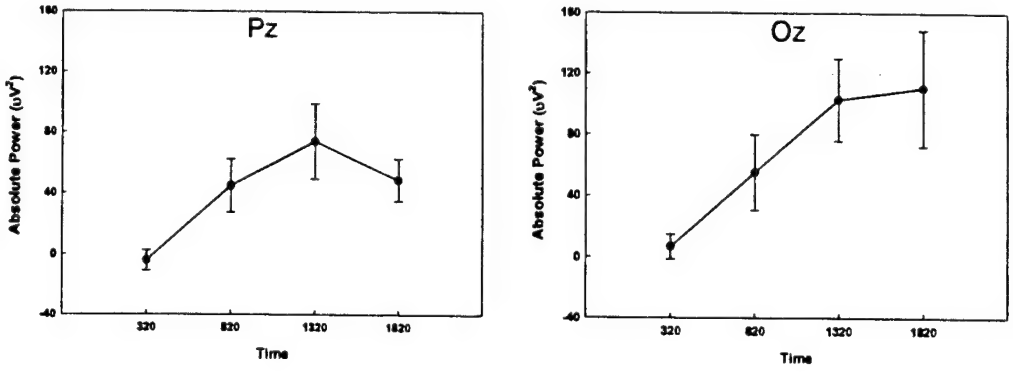

Figure 11. The overall effects of sleep deprivation (testing time) on resting EEG delta activity at Pz (left) and Oz (right).

Theta activity

The analysis of the percentage-change-from-baseline in absolute theta power (3.5-8.0 Hz activity) revealed a variety of effects. At Pz, there was a significant interaction among the condition, time, and eyes factors ($F(3,27)=3.40$, $p=.0321$) which analysis of simple effects attributed to a condition-by-time interaction at eyes closed ($p<.05$), but not at eyes open. Subsequent examination revealed that, in this case, there was a greater increase in theta under placebo versus modafinil at 0820 and 1320, but not at the other testing times ($p<.05$) (see figure 12).

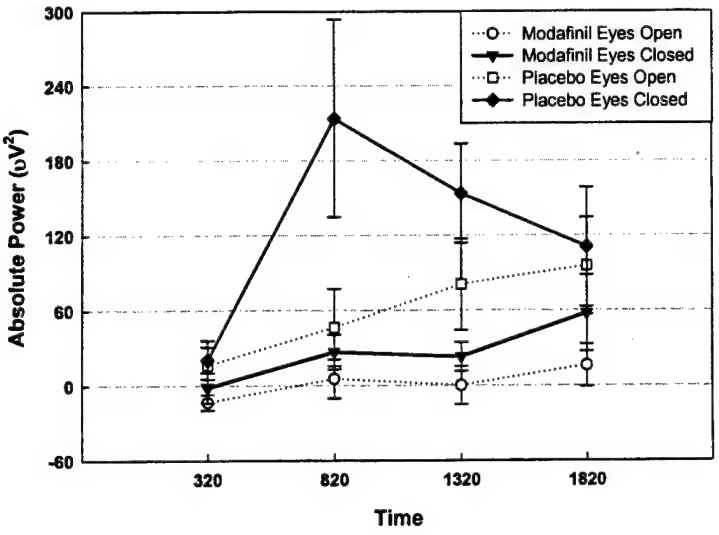

Figure 12. The interactive effects of condition, testing time, and eye closure on resting EEG theta activity at Pz.

In addition to the three-way interaction, there were significant time-by-eyes effects at Pz ($F(3,27)=3.05$, $p=.0457$) and Oz ($F(2.54,22.84)=3.36$, $p=.0428$). Both of these were due to a greater increase in theta under eyes-closed (relative to baseline) than under eyes-open at 0820 ($p<.05$) while similar effects were not observed at the other testing times. Figure 13 shows these effects.

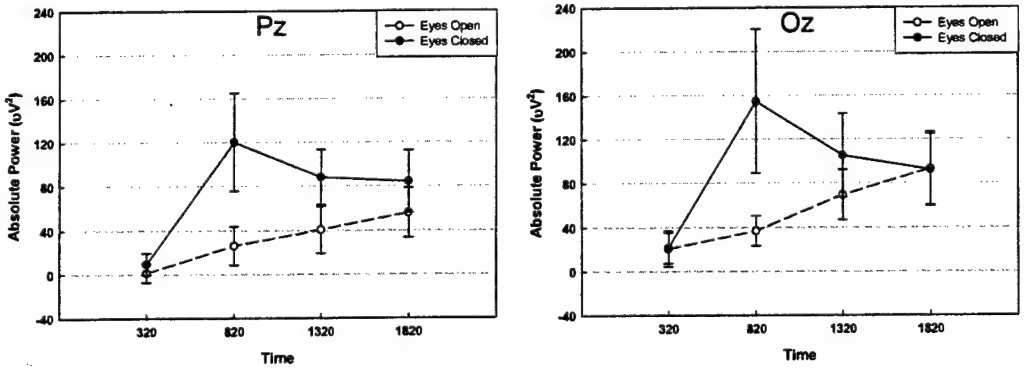

Figure 13. The combined effects of testing time and eyes on resting EEG theta activity at Pz (left) and Oz (right).

One other statistically-significant interaction was found at Oz, and in this case, it was between condition and time ($F(3,27)=3.66$, $p=.0247$). Analysis of simple effects

revealed this two-way interaction was due to a substantially larger increase in theta under placebo than under modafinil (relative to baseline) at 1320 and at 1820, but not at the other testing times ($p<.05$) (see figure 14).

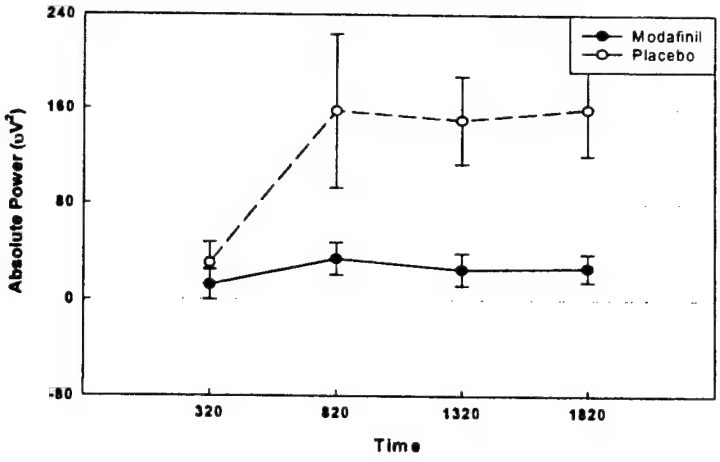

Figure 14. The combined effects of treatment condition and testing time on resting EEG theta activity at Oz.

In addition to the interactions observed within the theta band, there were main effects on the condition factor at Cz ($F(1,9)=10.69$, $p=.0097$), Pz ($F(1,9)=9.15$, $p=.0144$), and Oz ($F(1,9)=6.58$, $p=.0305$). All of these were due to substantially more theta under placebo (relative to baseline) than under modafinil (see figure 15).

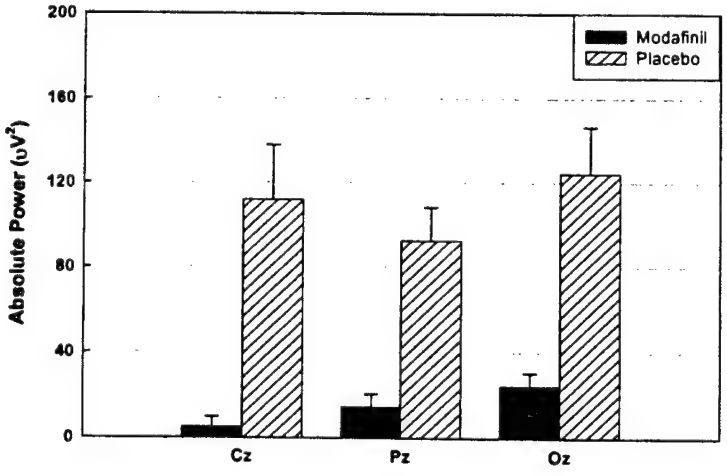

Figure 15. The overall effects of treatment condition (modafinil versus placebo) on resting EEG theta activity at Cz, Pz, and Oz.

In addition, there were main effects on the time factor at Pz ($F(3,27)=3.87$, $p=.0201$) and Oz ($F(3,27)=3.30$, $p=.0354$). At Pz, the overall time effect was due to a linear increase in theta activity as a function of sleep deprivation ($p<.05$) as well as a quadratic trend that resulted from a particularly sharp increase in theta from 0320 to 0820 ($p=.05$). At Oz, the time main effect was due simply to a significant linear increase in theta activity as a function of fatigue ($p<.05$) (see figure 16.)

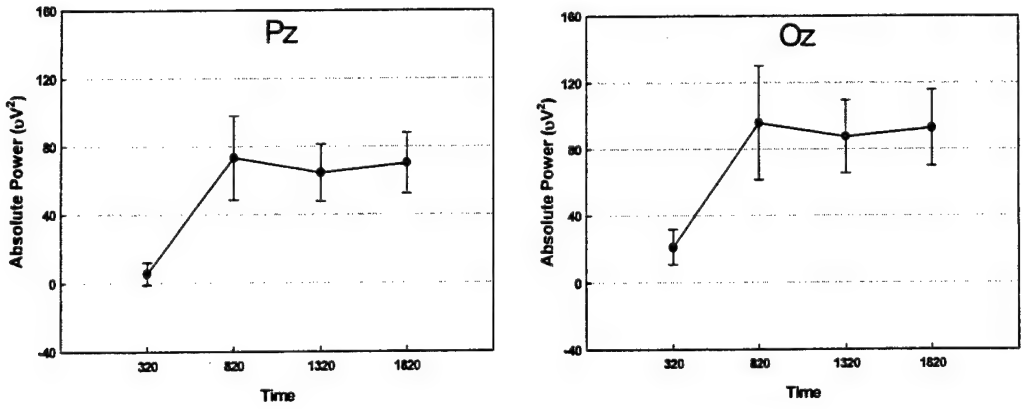

Figure 16. The effects of time on resting EEG theta activity at Pz (left) and Oz (right).

Alpha activity

The analysis of percent-change-from-baseline alpha power (8.0-13.0 Hz activity) indicated there were no condition or time main effects. There also were no interactions between condition and time. However, there was an interaction between testing time and eye closure at Cz ($F(2.35,21.21)=3.69$, $p=.0362$) and Pz ($F(2.13,19.19)=5.18$, $p=.0146$). Analysis of simple effects attributed the interaction to the presence of more alpha at eyes closed than at eyes open only during the 1320 and 1820 testing times ($p<.05$) (See figure 17). These findings are reflected in the overall eye-closure main effects observed at Cz ($F(1,9)=9.05$, $p=.0147$) and Pz ($F(1,9)= 5.68$, $p=.0409$). The means for eyes-open and

eyes-closed at Cz were 23.11 and -24.85, and at Pz, the means were 30.05 and -30.99, respectively.

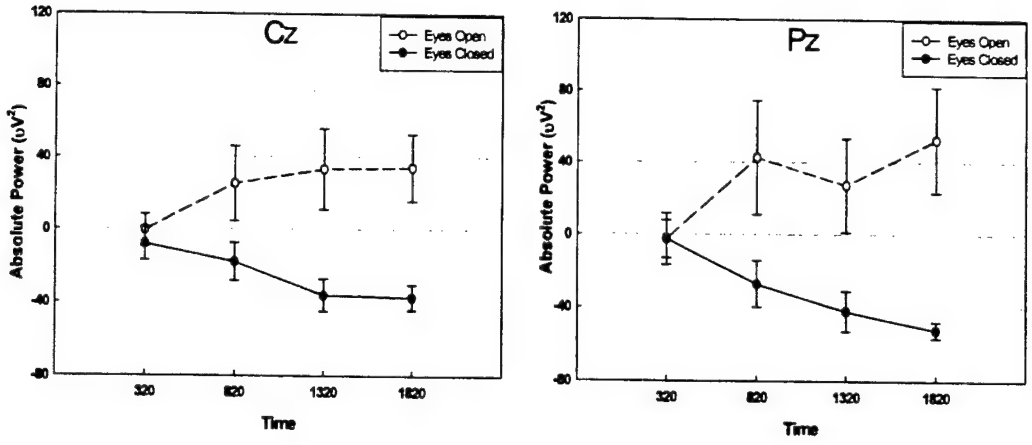

Figure 17. The combined effects of testing time and eye closure on resting EEG alpha activity at Cz (left) and Pz (right).

In addition to these statistically-significant results, there was a marginally-significant interaction between condition and eye-closure at Oz ($F(1,9)=4.83$, $p=.0555$). Analysis of simple effects revealed this was due to a tendency toward a greater increase in alpha activity under the placebo condition than under the modafinil condition at eyes open ($p=.11$), whereas a similar effect was absent at eyes closed (see figure 18).

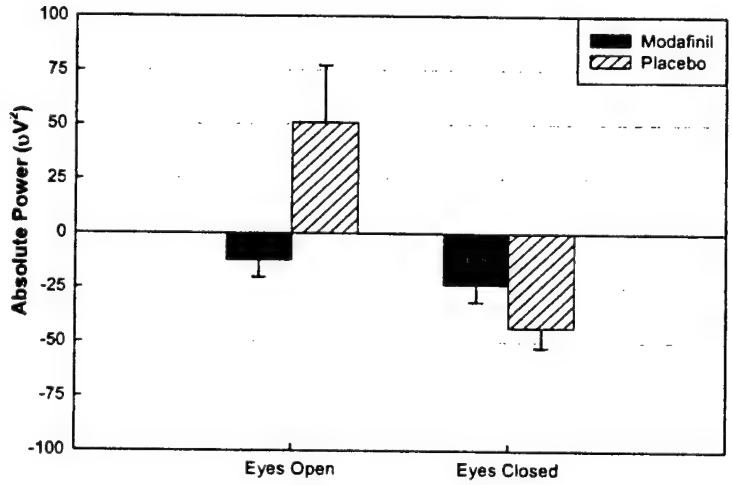

Figure 18. The marginally-significant interactive effects of treatment condition and eye closure on resting EEG alpha activity at Oz.

Profile of Mood States

The data collected on the POMS yielded six factor scores for each iteration of this test. The factor scores reflected self-ratings of anger-hostility, tension-anxiety, depression-dejection, vigor-activity, fatigue-inertia, and confusion-bewilderment. Prior to analysis, these data were transformed into percent-change-from-baseline scores (the 2230 test at the beginning of the respective deprivation periods was used as the baseline for the POMS). Afterwards, each set of factor scores was analyzed separately in six independent two-way ANOVAs to determine whether there were differences across the various deprivation testing times (0330, 0830, 1330, and 1830), and/or conditions.

Tension-anxiety

The two-way ANOVA of tension-anxiety scores indicated there were no condition or time main effects. In addition, there was no condition-by-time interaction.

Depression-dejection

The two-way ANOVA of baseline-corrected depression-dejection scores revealed both a condition-by-time interaction ($F(1.35,12.18)=4.41$, $p=.0480$) and a time main effect ($F(1.64,14.73)=4.58$, $p=.0343$). Analysis of simple effects indicated that the condition-by-time interaction was due to a tendency ($p=.0680$) towards increased depression scores under placebo versus modafinil at 0830, but not at the other testing times. Figure 19 shows the sharp increase in depression scores (relative to baseline) at this time. The overall time main effect was the result of a significant quadratic trend ($p<.05$) and a marginally-significant cubic trend ($p=.0572$). In general, depression ratings at 0330 were similar to those observed at the 2230 baseline, but the ratings at 0830 were

substantially higher, and despite a general decline, scores remained somewhat elevated at 1330 and 1830.

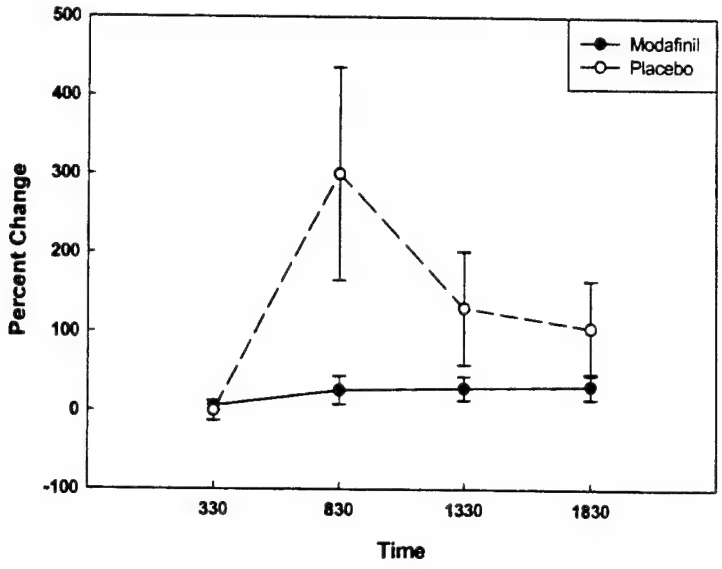

Figure 19. The interactive effects of treatment condition and testing time on POMS depression-dejection ratings.

Anger-hostility

The analysis of percent-change scores on the anger-hostility scale indicated there was a condition main effect ($F(1,9)=5.39$, $p=.0453$), but no time main effect and no condition-by-time interaction. The condition effect was due to the fact that anger ratings were only 4.09 percent higher than baseline under modafinil, whereas anger ratings were 42.9 percent higher under placebo (relative to baseline). The general impact of modafinil versus placebo is depicted in figure 20.

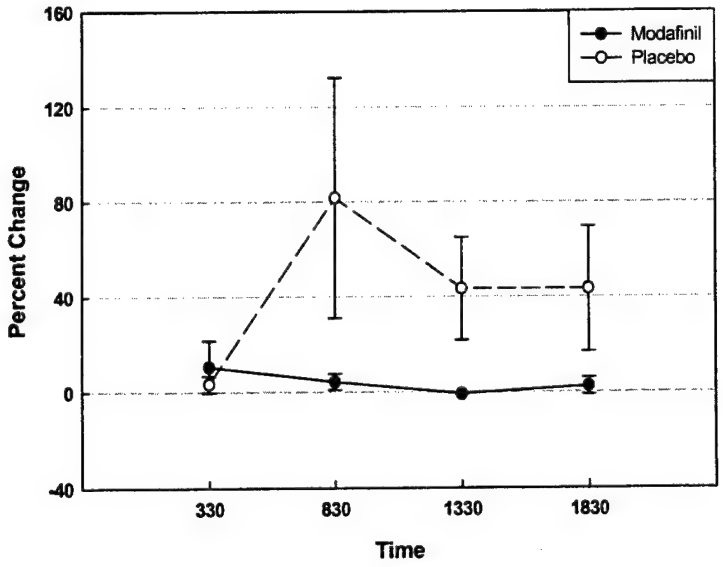

Figure 20. The overall impact of treatment condition (modafinil versus placebo) on POMS anger-hostility ratings.

Vigor-activity

The two-way ANOVA of percent-change vigor-activity scores revealed a condition main effect ($F(1,9)=13.00$, $p=.0057$) and a time main effect ($F(3,27)=13.92$, $p<.0001$), but no condition-by-time interaction. With regard to the condition effect, examination of the mean ratings showed that, under the influence of modafinil, vigor ratings fell from baseline by only 26.85 percent, whereas under placebo, vigor ratings fell by an average of 45.52 percent. Analyses of the effects across time revealed the presence of significant linear, quadratic, and cubic trends ($p<.05$) that resulted from a substantial initial drop in vigor scores from 0330 to 0830, a very slight increase from 0830 to 1330, and a subsequent leveling off from 1330 to 1830. The general timing of the changes in self-perceived vigor was similar under both treatment conditions (see figure 21).

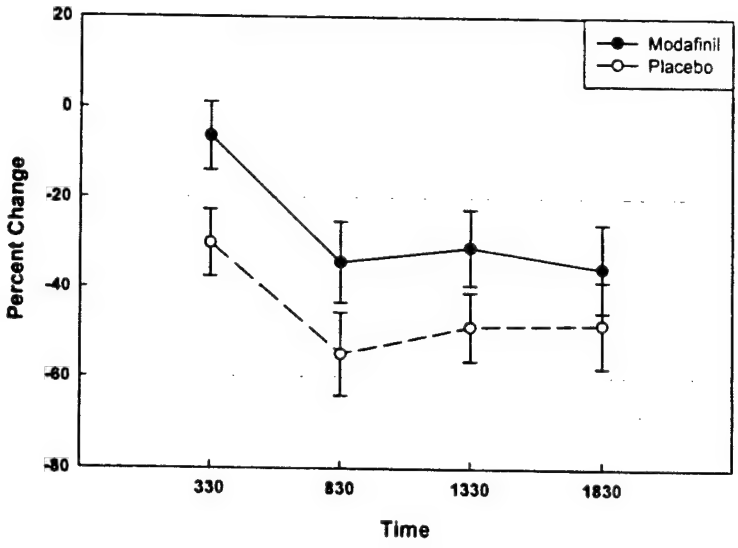

Figure 21. The separate impact of treatment condition (modafinil versus placebo) and sleep deprivation (testing time) on POMS vigor-activity ratings.

Fatigue-inertia

The analysis of the fatigue-inertia scale surprisingly revealed only a time main effect ($F(2.52,22.67)=5.09$, $p=.0104$) despite the fact that there was a 251 percent increase in self-rated fatigue under modafinil versus 511 percent under placebo. Apparently the large variability among participants' ratings was responsible for this lack of statistical significance. The time main effect was more in line with expectations in that it revealed a linear increase in self-rated fatigue throughout the sleep-deprivation period ($p<.05$) as well as a quadratic effect ($p<.05$) associated with the particularly-pronounced increase in fatigue that followed the 0330 test session. The effects of test times between the two conditions are illustrated in figure 22.

Confusion-Bewilderment

Similar to what was observed in the POMS fatigue scores, the two-way ANOVA on baseline-referenced ratings from the confusion-bewilderment scale revealed only a time main effect ($F(2.19,19.69)=3.99$, $p=.032$). Subsequent analysis indicated this was due to

the presence of a significant linear trend ($p<.05$) and a marginally-significant quadratic trend ($p<.055$). Examination of the overall means (with treatment conditions collapsed) showed a general increase in confusion-bewilderment from 0330 to 1830, with a particularly steep increase from 0330 to 0830 (see figure 23).

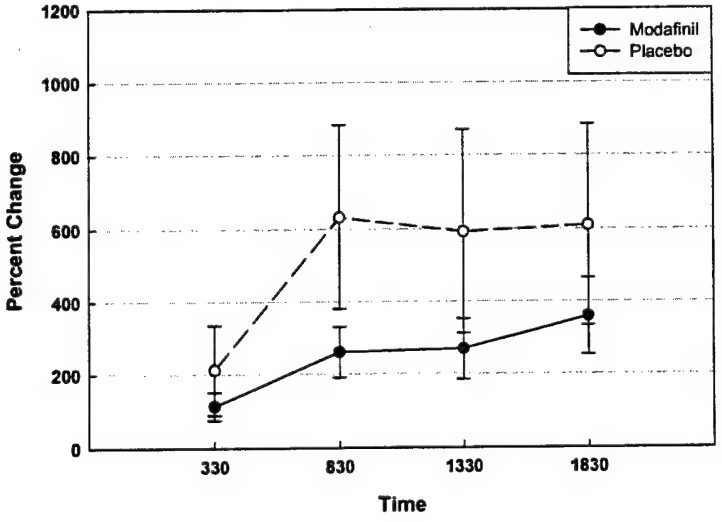

Figure 22. The impact of sleep deprivation (testing time) and condition on POMS fatigue-inertia ratings.

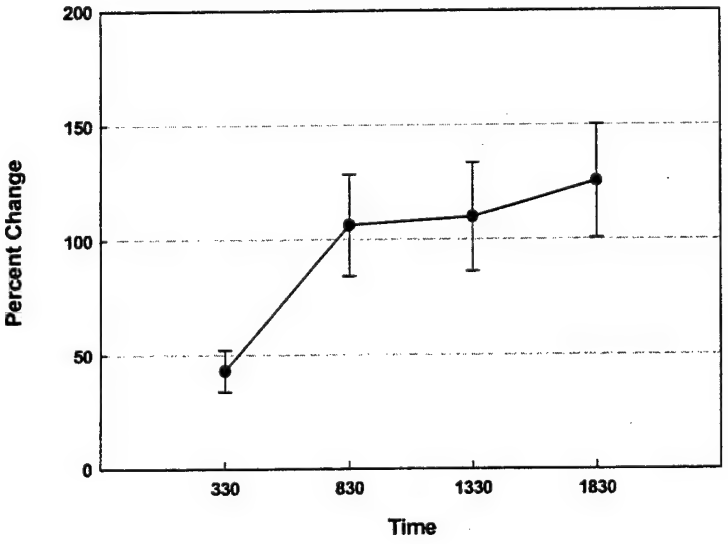

Figure 23. The overall impact of sleep deprivation (testing time) on POMS confusion-bewilderment ratings.

Visual Analog Scale

There were a total of eight different VAS measures collected during each iteration of this test (VAS testing immediately followed POMS administration). The VAS scores reflected self-ratings of alertness, anxiety, energy, confusion, irritability, jitteriness, sleepiness, and talkativeness. Prior to analysis, these data were transformed into percent-change-from-baseline scores using the 2230 test (from the beginning of each respective modafinil/placebo sleep-deprivation cycle) as the baseline. Afterwards, each VAS measure was analyzed in separate two-way ANOVAs to determine whether there were differences on each scale across the various sleep-deprivation testing times (0330, 0830, 1330, and 1830).

Alertness

Analysis of the percent-change-from-baseline in alertness scores revealed an overall condition main effect ($F(1,9)=20.77$, $p=.0014$) as well as a time main effect ($F(1.98,17.80)=8.30$, $p=.0029$). The condition effect was due to the fact that, compared to baseline, self-perceived alertness fell by an average of only 22.68 percent under the modafinil condition, while under placebo, alertness ratings dropped by 40.81 percent. The time effect occurred because of an overall linear decline in alertness ratings that was especially dramatic from 0330 to 0830 ($p<.05$). In addition, there was a significant quadratic trend ($p<.05$) because, after the initial drop in self-rated alertness, the participants continued to feel less alert for the remainder of the sleep-deprivation period. This effect is depicted in figure 24, top left.

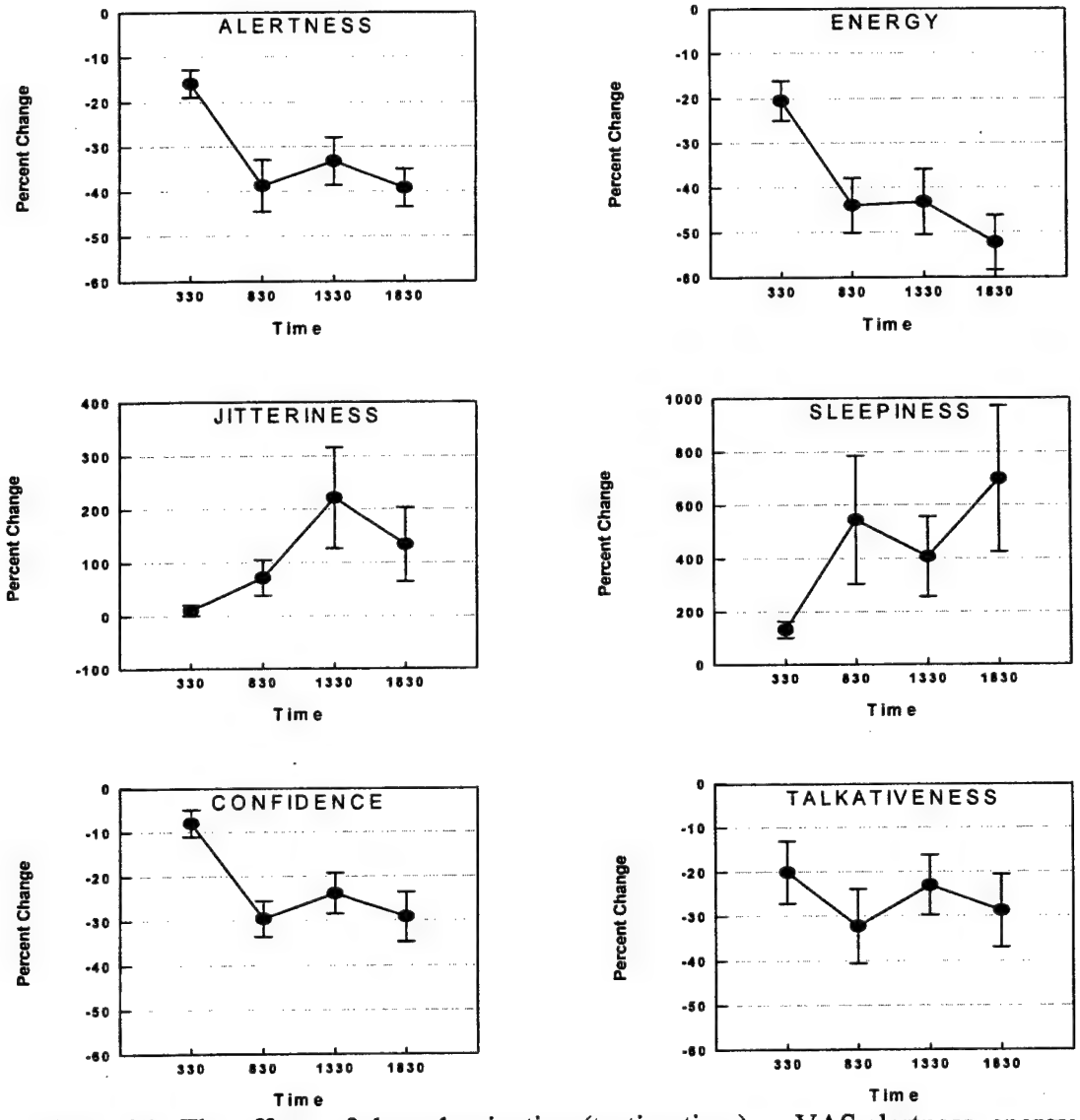

Figure 24. The effects of sleep deprivation (testing time) on VAS alertness, energy, jitteriness, sleepiness, confidence, and talkativeness ratings.

Energy

The percent-change energy ratings revealed a condition main effect ($F(1,9)=17.30$, $p=.0025$) and a time main effect ($F(3,27)=13.06$, $p<.0001$). The condition effect resulted from the fact that self-perceived energy fell by only 30.34 percent under modafinil, whereas there was a full 49.6 percent decrease under placebo. The time main effect resulted from an overall linear decrease in self-perceived energy from the 0330 to the

1830 session ($p<.05$). In addition, there was a marginally-significant cubic trend ($p<.0595$) that reflected a "leveling off" of energy ratings between 0830 and 1330, prior to a further deterioration from 1330 to 1830 (see figure 24, top right).

Anxiety

The VAS anxiety ratings were found to be unaffected by either treatment condition or by the various testing times. Also, there was no interaction between condition and time.

Irritability

VAS ratings of irritability likewise were not differentially affected by condition, time, or the combination of condition and time.

Jitteriness

Similar to what was observed in terms of self-perceived anxiety and irritability, percent-change ratings on the jitteriness scale revealed no statistically-significant effects. There was a marginal time main effect ($p=.0612$), but it was not further explored. However, the tendency toward time-dependent changes in this scale are presented in figure 24, middle left.

Sleepiness

VAS ratings (percent-change-from-baseline) on the sleepiness dimension surprisingly did not show a significant main effect on the condition factor, nor was there a condition-by-time interaction; however, there was a significant effect on the time factor ($F(1.65,14.87)=4.15$, $p=.0433$). Analysis of the time effect indicated a linear increase in sleepiness relative to baseline ($p<.05$) as shown in figure 24 (middle right).

Confidence

Baseline-referenced self-ratings on confidence revealed a significant condition main effect ($F(1,9)=14.62$, $p=.0041$) and a significant time main effect ($F(3,27)=9.70$, $p=.0002$); however, as was the case with several other VAS scales, there was no condition-by-time interaction. The condition main effect was due to the fact that self-rated confidence decreased by an average of only 16.44 percent under the modafinil condition, whereas it decreased by 28.77 percent under the placebo condition. The time main effect was due to the fact that confidence ratings declined in a linear fashion from the beginning to the end of the deprivation period ($p<.05$). In addition, the presence of significant quadratic and cubic trends ($p\leq.05$) revealed that perceived confidence declined most noticeably from 0330 to 0830, after which time confidence ratings remained lower than baseline for the remainder of the sleep-deprivation period (see figure 24, bottom left).

Talkativeness

Self-ratings on VAS talkativeness were affected only by testing time as indicated by the presence of a significant main effect on the time factor ($F(3,27)=3.18$, $p=.0400$). Trend analysis showed the existence of a cubic effect that resulted from a reduction in self-perceived talkativeness from 0330 to 0830, a slight recovery from 0830 to 1330, and then a slight decline from 1330 to 1830 ($p<.05$). This overall time effect is shown in figure 24, bottom right.

In-flight (simulator) EEG

In addition to the resting EEG that was conducted under standard laboratory conditions, EEG data were collected while the participants were in the simulator flying

the maneuvers discussed earlier. Unfortunately, a review of these data indicated that they were quite contaminated by artifacts that were impossible to eliminate without constantly reminding the pilots to minimize eye movements and eye blinks while relaxing their jaw and neck muscles. Since such constant coaching would have distracted the pilots from their primary flight tasks, possibly confounding the test results, the investigators chose to minimize these admonishments. As a result, data from two of the participants had to be entirely excluded due to artifact, and there were instances in which almost 30 percent of the data from the remaining eight participants required estimation in order to achieve the complete cases required by BMDP4V. Since, in all probability, these case exclusions and data estimations compromised the integrity of the in-flight EEG results, the ANOVAs conducted on in-flight delta, theta, and alpha activity will not be reported here. Instead, efforts will be undertaken in the near future to have these data analyzed by a laboratory equipped with software routines capable of removing the observed recording artifact.

Simulator Flight performance

Prior to analysis, the data collected from each of the simulator flights were transformed into percentage-of-change-from-baseline accuracy scores by calculating comparisons between the deprivation flights at 0400, 0900, 1400, and 1900 and the deprivation flight at 2300 (this was done for both the modafinil sleep-deprivation cycle and the placebo sleep-deprivation cycle). These percent-change data were first analyzed separately for each maneuver and then combined into a single overall analysis that included all of the maneuvers together. The separate analyses for the majority of the flight maneuvers consisted of two-way ANOVAs across the two treatment conditions (modafinil, placebo) and the four testing times (0400, 0900, 1400, and 1900). However,

the two right 360° turns and the five straight-and-levels were analyzed with three-way ANOVAs because there was more than one iteration of each of these maneuvers in the flight profile. Thus, for the right turns and the straight and levels, there were three design factors—treatment condition, maneuver iteration, and testing time.

In order to conduct the overall analysis in which all maneuvers were equivalently examined together, the two iterations of the right turn and the five iterations of the straight-and-level were simply averaged together (via BMDP transformations) so that there would be the same amount of data for these two maneuvers as for the other six maneuvers (in which there was only one iteration for each maneuver).

Straight climb

Analysis of the straight climb from 11,000 to 13,000 feet revealed a condition main effect ($F(1,9)=6.18$, $p=.0347$) and a time main effect ($F(3,27)=3.06$, $p=.0453$). The condition effect was attributable to a much smaller change from baseline in composite flight performance under modafinil than under placebo (the means across all flights were -29.76 for modafinil and -62.69 for placebo). Obviously, overall performance was better when fatigue was being treated by the drug than when no intervention was administered. The time main effect was due to the fact that overall flight performance was progressively impaired by continuous wakefulness. Trend analysis indicated the presence of marginally significant linear ($p=.08$) and quadratic ($p=.07$) trends which were due to a tendency toward an especially pronounced performance decrement (relative to baseline) from 0400 to 0900, after which performance remained degraded until the last flight of the day. Both the condition and time effects are depicted in figure 25.

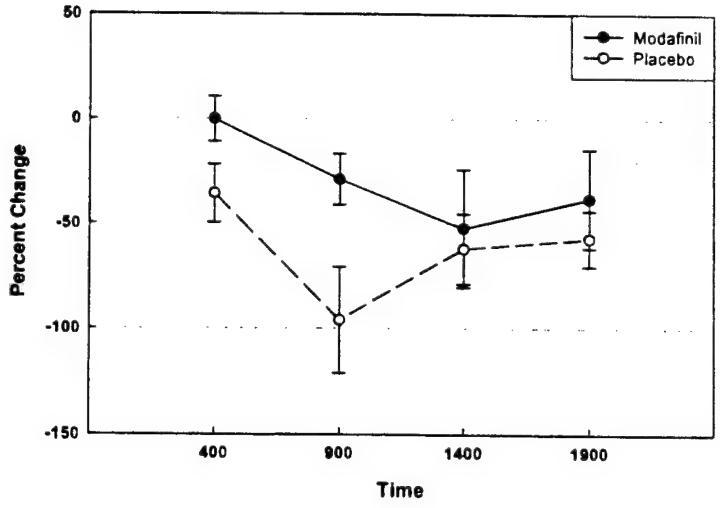

Figure 25. The non-significant effects of treatment condition and testing time on performance of the straight climb.

Straight descent

Percent-change scores from the maneuver in which participants descended from 15,000 to 13,000 feet on a consistent heading of 345° indicated no changes from baseline as a function of treatment condition or testing time. Although figure 26 seems to suggest that overall performance was better under modafinil than under placebo, the difference was not statistically significant (p=.1311).

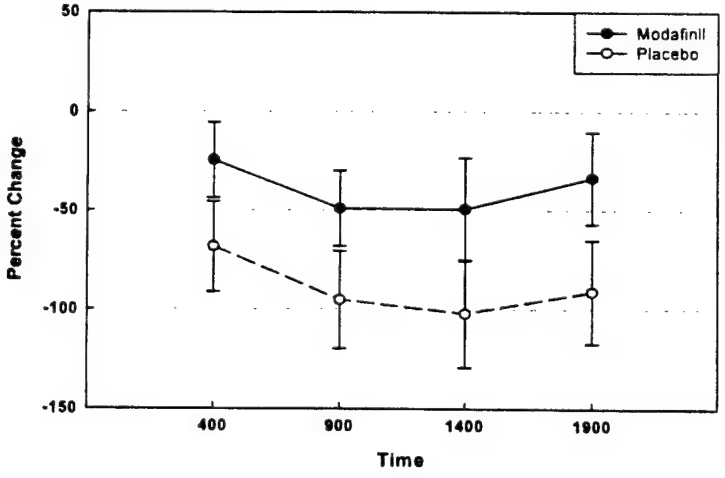

Figure 26. The independent effects of treatment condition and testing time on performance of the straight descent.

Left 720° turn. The data from the 720° left turn at 15,000 feet revealed a significant condition-by-time effect ($F(2.36,21.23)=4.05$, $p=.0270$), a significant condition main effect ($F(1,9)=7.62$, $p=.0221$), and a significant time main effect ($F(2.44,21.92)=4.06$, $p=.0252$). Analysis of simple effects indicated the interaction was due to the absence of a difference between modafinil and placebo at 0400 followed by significant differences at 0900, 1400 ($p<.05$), and marginally, at 1900 ($p=.08$). The time main effect was due to a quadratic trend in the data that resulted from a substantial reduction in flight accuracy at 0900 in comparison to the other three flights. The condition main effect was attributable to the fact that performance under modafinil was generally better than performance under placebo (the means were -23.24 and -104.45, respectively). Figure 27 graphically depicts the impact of both treatment condition and time on the performance of this maneuver.

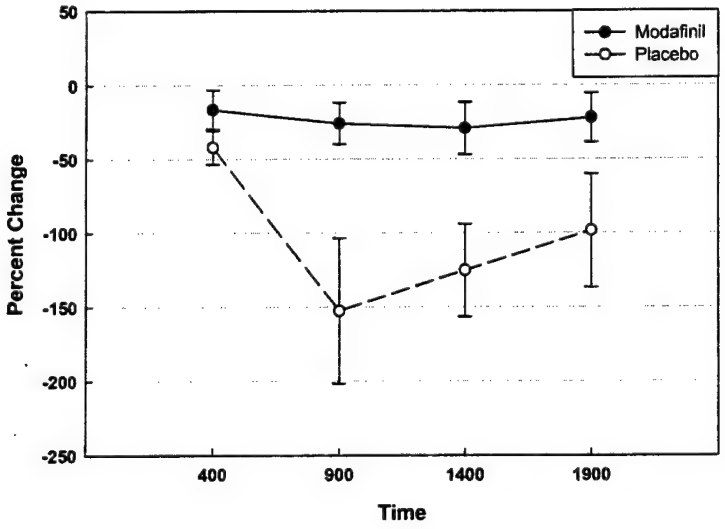

Figure 27. The interactive effects of both treatment condition and sleep deprivation on performance of the left 720-degree turn.

Left climbing turn

Analysis of the data from the maneuver in which participants were required to climb from 10,000 to 15,000 feet while simultaneously executing a 540° turn indicated a

significant condition main effect ($F(1,9)=8.01$, $p=.0197$), but no time main effect or condition-by-time interaction. The condition effect was due to less degradation from baseline under modafinil (i.e., more stable performance) than under placebo (the means were -34.95 and -103.71, respectively). This pattern is depicted in figure 28. Note that, although the degradation in performance that occurred simply as a function of time appears rather pronounced in these data, the effect was not significant ($p=.09$).

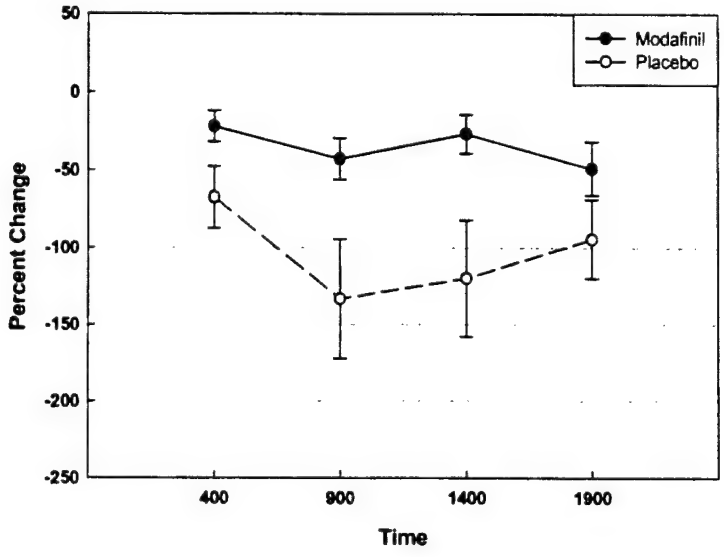

Figure 28. The independent impact of treatment condition (modafinil versus placebo) on performance of the left climbing turn.

Left 360° turn

Analysis of the 360° left turn that was performed at an altitude of 11,000 feet revealed no differences as a function of condition, time, or the combination of the two factors. As shown in figure 29, there was a substantial amount of variability in the performance of this maneuver at 1400, primarily under the placebo condition. This is because one participant fell asleep at the controls as a function of fatigue, and as a result, he lost 848 feet of altitude before he spontaneously awoke and regained control of the simulator.

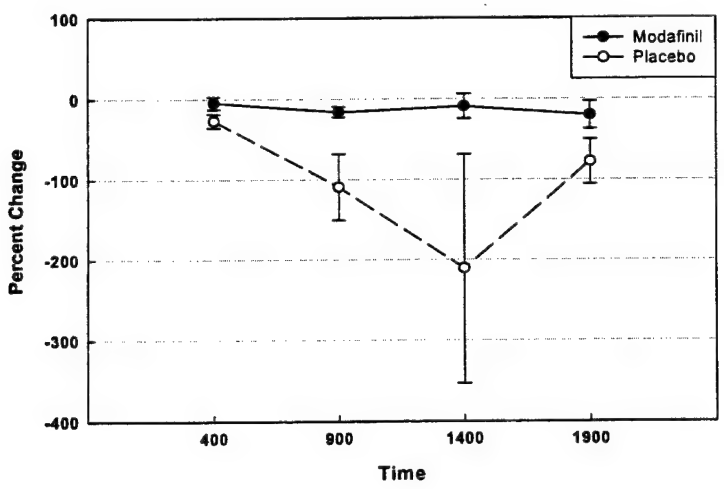

Figure 29. The non-significant pattern of condition and time effects on performance of the left 360-degree turn.

Right descending turn

Analysis of the maneuver in which participants descended from 13,000 to 10,000 feet while simultaneously executing a 360° turn revealed no condition-by-time interaction and no time main effect; however, there was a marginally-significant condition main effect ($F(1,9)=4.69$, $p=.0586$). As shown in figure 30, there tended to be less deviation from baseline performance under the modafinil condition than under the placebo condition (the means were -40.11 and -74.78, respectively).

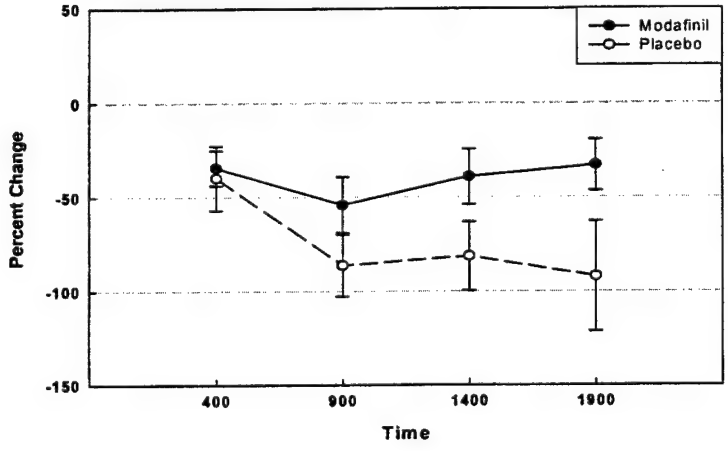

Figure 30. The marginally-significant interactive effects of treatment condition and sleep deprivation (testing time) on the performance of the right descending turn.

Right 360° turn

The combined analysis of the first 360° right turn (that was performed at an altitude of 11,000 feet) and the second 360° right turn (that was flown at an altitude of 15,000 feet) revealed no main effects on the time or maneuver factors and no interactions involving condition, time, or maneuver. However, as was the case several times earlier, there was a condition main effect ($F(1,9)=6.65$, $p=.0297$) which was due to the fact that performance degraded less under modafinil (relative to baseline) than under placebo (the means were -22.11 and -58.05, respectively). This overall difference between the two treatment conditions is shown in figure 31.

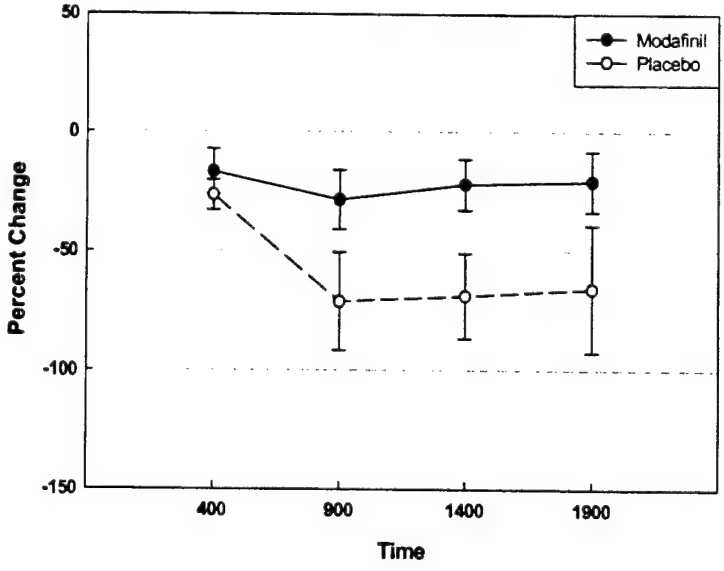

Figure 31. The overall impact of treatment condition (modafinil versus placebo) on the performance of the right 360-degree turn.

Straight and levels

Like the ANOVA on the two right 360-degree turns, the three-way ANOVA on all five straight-and-levels revealed that there were no main effects on the time or maneuver factors and no interactions involving condition, time, or maneuver. However, there was

an overall condition main effect (F(1,9)=8.80, p=.0158) that resulted from better performance under modafinil than under placebo (the respective means for each condition were -16.78 and -60.68). As can be seen in figure 32, modafinil maintained control accuracy almost at baseline levels, whereas placebo did not.

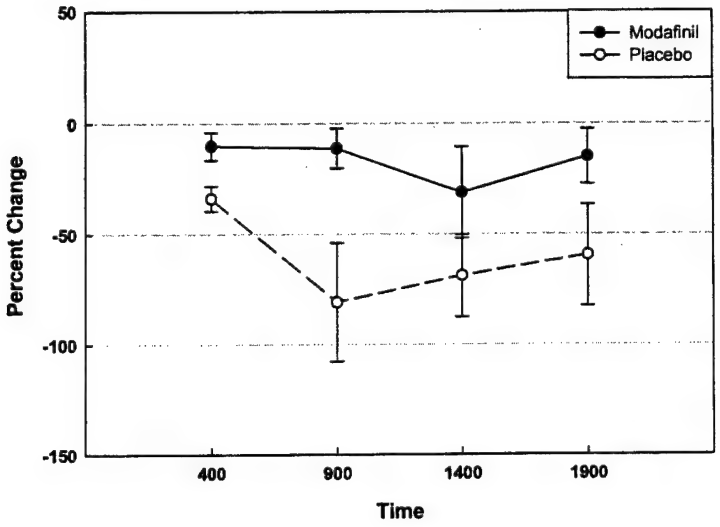

Figure 32. The overall impact of treatment condition (modafinil versus placebo) on the performance of the straight-and-level maneuvers.

Composite flight performance

The three-way ANOVA that examined the impact of treatment condition (modafinil, placebo), testing time (0400, 0900, 1400, and 1900), and flight maneuver on basic piloting skill across all of the flight maneuvers considered together, revealed two main effects and no interactions. The first main effect involved the condition factor (F(1,9)=9.29, p=.0138) and the second involved the time factor (F(2.95,26.58)=4.56, p=.0108). With regard to the condition effect, examination of the mean modafinil/placebo data indicated that, relative to baseline, performance under modafinil (with all flight times collapsed) only degraded an average of 27 percent whereas performance under placebo fell by an average of approximately 82 percent. With regard

to the time effect, trend analysis revealed that the overall impact of continuous wakefulness (regardless of whether modafinil or placebo was given) was more severe at the 0900 and 1400 flights than at the 0400 and 1900 flights (the quadratic trend was significant at p=.0149). The general performance characteristics across all maneuvers as a function of condition, as well as the interaction between condition and time, are depicted below in figure 33.

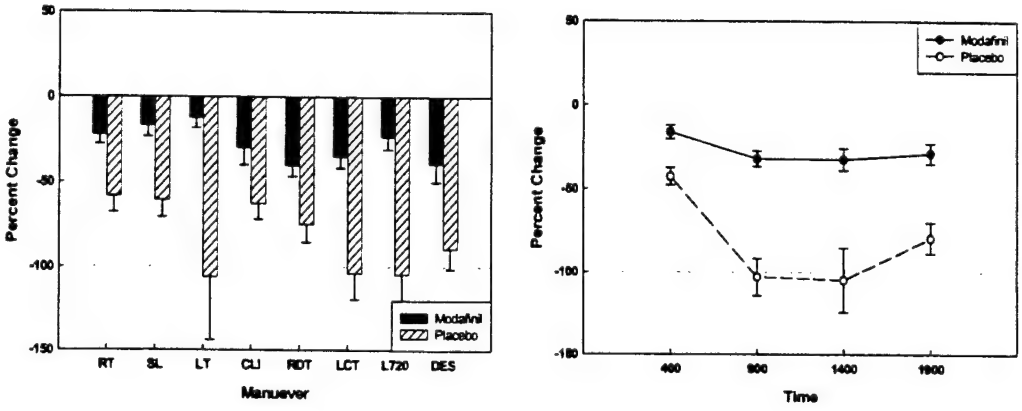

Figure 33. The overall effects of treatment condition on each maneuver (left) and the general effect of sleep deprivation across all maneuvers combined (right).

Simulator Sickness Questionnaire

The percent-change SSQ factor scores for nausea, visuomotor problems, disorientation, and total-problem-severity were analyzed via a two-way ANOVA for condition (modafinil, placebo) and testing time (0335, 0835, 1335, and 1835). This was done only on the data from the five newly-recruited subjects since no SSQ data were available from the first deprivation cycle in which the re-recruited participants were tested (the SSQ was not administered in the previously-conducted fatigue study).

There were no condition-related effects on any of the four SSQ factors, but there were statistically-significant time effects on both the visuomotor symptoms (eye-strain symptoms including headache) and the total-problem-severity scores (general

discomfort). For the visuomotor score, the ANOVA results were: F(2.56,10.22)=5.00, p=.0252; and for the total-problem-severity scores, the ANOVA results were: F(2.73,10.91)= 3.71, p=.0490. Subsequent trend analysis was not helpful for further illuminating the nature of these time effects as none of the trends attained statistical significance (probably because of insufficient power due to the small sample size of 5). However, the data are graphically depicted to show the non-significant tendencies (see figure 34).

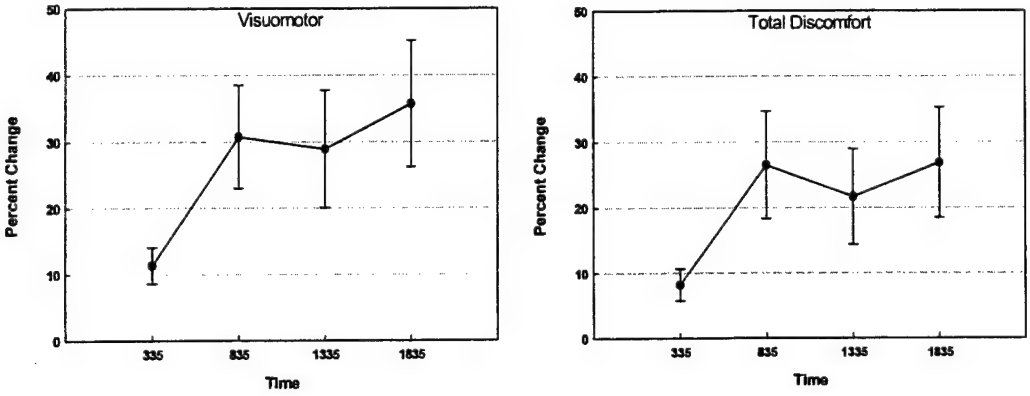

Figure 34. The general impact of sleep deprivation (testing time) on visuomotor scores (left) and total-discomfort scores (right) on the SSQ.

Side Effects Questionnaire

The following symptom categories were summarized for each treatment condition (frequency counts were calculated with Excel™): 1) *drugged feeling*, 2) *light headedness*, 3) *loss of coordination*, 4) *nausea*, 5) *vertigo*, 6) *confusion*, and 7) *headache*. Only the side-effects ratings from the newly-recruited participants were evaluated since the re-recruited participants were not administered this questionnaire during the earlier fatigue study in which they participated (since there was no drug intervention in that study, no side effects were possible). As shown in table 6, few side effects were reported.

Table 6. Side effects reported under the modafinil and placebo conditions

Symptom	Severity	Modafinil	Placebo
Drugged feeling	Slight	2 (1 person)	3 (2 people)
	Moderate	1 (1 person)	3 (1 person)
Light-headed	Slight	1 (1 person)	0
	Moderate	0	0
Loss of coordination	Slight	2 (2 people)	4 (2 people)
	Moderate	0	0
Nausea	Slight	3 (1 person)	0
	Moderate	0	0
Vertigo	Slight	0	1 (1 person)
	Moderate	0	0
Confusion	Slight	2 (1 person)	2 (1 person)
	Moderate	0	1 (1 person)
Headache	Slight	2 (1 person)	4 (2 people)
	Moderate	0	2 (1 person)
Total	*Slight/Moderate*	*11*	*14*

DISCUSSION

The fatigue associated with continuous and sustained aviation operations can pose a serious threat to the mood, performance, and operational readiness of pilots (Perry, 1974). In fact, without effective countermeasures, fatigue-related problems can degrade performance by more than 40 percent after as little as 24-40 hours of continuous

wakefulness, or one night of sleep loss (Angus and Heslegrave, 1985). This is why, for years, the U.S. military has periodically depended upon dextroamphetamine to preserve the mission readiness of fatigued pilots in combat operations that are devoid of adequate restorative sleep opportunities (Cornum, Caldwell, and Cornum, 1997). Both field experience and laboratory studies have proven that properly-administered dextroamphetamine offers a safe and effective way to sustain the performance, mood, and physiological alertness of sleep-deprived aviation personnel (Caldwell, Caldwell, and Darlington, 2003). However, despite the benefits of dextroamphetamine, there are drawbacks related to the fact that this drug is known to elevate heart rate and blood pressure (Martin et al., 1971), and it is known to pose a risk of abuse that can lead to psychological or physical dependence in a subset of susceptible individuals (Akerstedt and Ficca, 1997).

For these reasons, the newer alertness-enhancing compound modafinil (Provigil®) has been viewed with increasing interest (Lyons and French, 1991). Several studies already have established that modafinil attenuates the impact of fatigue in sleep-deprived personnel (i.e., Lagarde and Batejat, 1995; Pigeau et al., 1995), and one study in particular has shown that modafinil holds significant promise for countering the effects of sleep loss in pilots (Caldwell et al., 2000). Unfortunately, however, there have been reports of problematic side effects (i.e., headache, nausea, etc.) that could limit the use of modafinil in aviation settings. Furthermore, the efficacy of modafinil for sustaining the performance of military jet pilots has not been clearly established in a systematic and objective manner. As a result, the Air Force has been hesitant to add modafinil to the approved armament of authorized aviator fatigue countermeasures.

The present quasi-experimental, single-blind, counterbalanced study sought to overcome this problem by objectively assessing the efficacy of modafinil versus placebo (or no treatment) for attenuating the impact of long hours of sustained wakefulness on current, active-duty F-117 pilots. In this investigation, pilot cognition, mood, physiological arousal, and flight performance were systematically assessed under both modafinil versus placebo/no-treatment throughout the latter part of 37-hour periods of continuous wakefulness. Potential modafinil-related adverse effects were examined via the periodic administration of a side-effects questionnaire and a simulator-sickness questionnaire.

General Fatigue Effects

In terms of the general impact of sleep loss (regardless of the treatment condition), the results of the present study were consistent with those from our earlier evaluation of sleep-deprived F-117 pilots (Caldwell et al., 2003). Untreated fatigue produced robust degradations in basic cognitive performance, mood, and objectively-measured flight performance. This was especially true in the control condition when modafinil administration was absent. As was the case in the earlier F-117 study, the greatest difficulties often occurred well after the presumed time of the circadian trough. Even though evaluations were conducted during the predawn hours (from 0200 to 0400), the most pronounced mood and cognitive deteriorations were seen much later during the 0700-0900 testing session (after 24-26 hours of continuous wakefulness). This was the case for MATB communications, systems-monitoring, fuel-monitoring, and tracking; POMS depression, fatigue, vigor, and confusion; and VAS alertness, energy, confidence, and talkativeness.

Within the flight data, the same general pattern was observed in the timing of noteworthy fatigue effects. Whereas flight performance at 0400 tended to be only slightly less accurate than performance during the earlier baseline flight (at 2300), control accuracy declined sharply at either the 0900 flight or the 1400 flight (after 26-31 hours of continuous wakefulness). As was the case in the earlier F-117 fatigue study, these later flight times corresponded to the times at which slow-wave EEG activity (an indicator of physiological fatigue) became noticeably elevated as well.

Taken together, the findings from the present investigation are not only consistent with those from our earlier assessment of untreated fatigue in F-117 pilots (Caldwell et al., 2003), but they are generally consistent with our previous evaluations of fatigue in sleep-deprived UH-60 helicopter pilots as well (Caldwell and Roberts, 2000). In both cases, the most serious fatigue-related decrements often occurred well after the predawn hours, although they were later in the F-117 pilots tested here than in the UH-60 pilots tested earlier (probably because the F-117 pilots normally worked later duty shifts than the helicopter pilots).

Efficacy of modafinil

Modafinil attenuated many of the negative effects of sleep loss. All combined, about half of the performance, mood, and other components examined in this study were significantly affected (improved) by modafinil administration. More to the point, of the 26 mood, performance, and physiological components found to be most sensitive to the effects of fatigue (as evidenced by the presence of either a time main effect or a time-related interaction), 16 of them were positively influenced by modafinil (in one case, the effect was marginal at $p<.06$). This is a total of 62 percent. In addition, there were 8

other instances (one of which was marginal at $p<.06$) in which modafinil helped to mitigate the serious impact of sleep deprivation.

Cognitive effects

From the standpoint of basic cognitive performance, modafinil was beneficial for reducing fatigue-related increases in the number of missed "radio calls" as well as the sleepiness-related increases in MATB tracking deviations. These positive effects were especially noticeable and consistent during the 0700-0900 testing session (after 24-26 hours of continuous wakefulness), although performance benefited well beyond that point. These results are consistent with the earlier findings of Caldwell et al (1999) and Wesensten et al (2002) who demonstrated that modafinil (in 100- or 200-mg doses) attenuated fatigue-induced vigilance decrements and/or tracking errors. From an operational standpoint, such effects are important because pilots depend on a high degree of vigilance and accuracy in order to safely conduct their flight missions, and these cognitive tests theoretically tap into these capabilities.

Physiological status

In terms of the physiological impact of sleep deprivation, modafinil administration was associated with an overall reduction in the slow-wave EEG activity that has been found to occur with increased sleepiness in untreated personnel (Pigeau, et al., 1987). In addition, modafinil prevented the reductions in saccadic velocity and the decreases in pupil diameter that have been associated with fatigue from sleep deprivation (Russo et al., 2003; Stern, 1999). In this study, modafinil significantly attenuated the fatigue-related accentuations of both delta activity (1.5-3.5 Hz) and theta activity (3.5-8.0 Hz) that were observed across all three of the midline EEG recording sites (Cz, Pz, and Oz).

Modafinil also sustained saccadic velocity at or above baseline levels throughout the testing period and attenuated the fatigue-related reductions in pupil diameter that were evident under the placebo/no-treatment condition. The efficacy of modafinil appeared as early as 0315 (after only 20 hours of continuous wakefulness) in the saccadic-velocity data and by approximately 0800 (after about 26 hours of continuous wakefulness) in the pupil-diameter and EEG data.

Although the beneficial effects of modafinil on oculomotor parameters have not to our knowledge been previously published elsewhere, the modafinil-related EEG effects are consistent with those reported from an earlier helicopter-pilot evaluation of this compound (Caldwell et al., 2000). In the present study as well as in the previous helicopter study, modafinil enhanced physiological alertness (relative to placebo or no-treatment) from as early as 0300 and continued to exert an effect throughout most of the remaining continuous-wakefulness period. From an operational perspective, these results suggest modafinil will reduce the generalized decrements on cognitive performance as well as the reduced responsiveness to incoming information that have been associated with the presence of increased slow-wave EEG activity (Belyavin and Wright,1987; Ogilvie and Simons, 1992). The occulomotor effects suggest a potential benefit in terms of countering the negative neuronal changes that can lead to decreased motivation, reduced attention, and impaired processing speed in fatigued personnel (Balkin et al., 2000).

Subjective ratings

With regard to self-reported mood and alertness, the 100 mg doses of modafinil used in this study attenuated feelings of depression-dejection and anger-hostility, while to

some extent mitigating a decline in feelings of vigor-activity that were associated with sleep deprivation. In addition, modafinil helped to preserve more normal (rested) self-perceptions of alertness, energy, and confidence despite the long bouts of sustained wakefulness. Approximately half of the self-report measures on which there were significant condition-related effects revealed a positive influence from modafinil after 20 hours of continuous wakefulness. The other half indicated beneficial effects after approximately 25 hours without sleep.

Interestingly, POMS fatigue and VAS sleepiness, while sensitive to the overall impact of sustained wakefulness, were unaffected by drug administration. Evidently, the effects of modafinil on mood are not as straightforward as those often reported with dextroamphetamine (Caldwell, Caldwell, and Darlington, 2003). For instance, although Pigeau et al. (1995) found reductions in fatigue-related mood disturbances after 300 mg modafinil; and Caldwell et al. (2000) reported improved vigor and reduced perceptions of fatigue in sleep-deprived pilots after 200 mg modafinil; Wesensten et al. (2002) failed to detect positive mood-related changes with 100, 200, or 400 mgs modafinil. Such discrepancies help to explain the fact that, when asked, the pilots in this study usually were unable to determine whether or not (or when) they had received the modafinil intervention. In fact, nine out of ten participants could not answer the question with any degree of certainty.

In light of these somewhat mixed results, the operational ramifications of the self-reported mood data remain unclear. On the one hand, the subjective experience of reduced depression and anger, coupled with increased vigor, alertness, energy, and confidence suggest that modafinil may enhance task motivation, increase optimism about

the ability to accomplish the mission, and improve cooperation and crew coordination. On the other hand, the failure to subjectively recognize modafinil-induced attenuations in fatigue and sleepiness may lead pilots to escalate the dose (increasing the chances of side effects) or to discontinue the drug altogether.

Simulator flight performance

In terms of the effects of modafinil on objectively-measured flight skills, the present results were favorable. In most cases, the pilots' abilities to precisely maintain target headings, altitudes, airspeeds, bank angles, and vertical velocities during the standardized flight profile were superior under the modafinil condition as opposed to the placebo/no-treatment condition. In fact, on six of the eight maneuvers--the straight climb, the left 720-degree turn, the left-climbing turn, the right 360-degree turns, the five straight-and-level segments, and (marginally) the right-descending turn—composite flight performance was far more accurate as a result of modafinil administration. Although the 100-mg doses of modafinil used in this study did not sustain performance at pre-sleep-deprivation levels as well as might have been expected with 10-mg doses of dextroamphetamine (based on Caldwell, Caldwell, and Darlington, 2003), an examination of mean composite accuracy at the 0400, 0900, 1400, and 1700 flights indicated that modafinil maintained control precision within approximately 15-30 percent of baseline levels. Flight performance under the no-treatment/placebo condition often declined by as much as 60-100 percent. Modafinil's effects were especially noticeable at the 0900 and 1400 flights (after 26-31 hours of sleep deprivation). These are the times at which our previous F-117 fatigue study (Caldwell et al., 2003) indicated the effects of fatigue were most severe.

Generally speaking, these positive results with F-117 pilots are consistent with the favorable effects previously seen with helicopter pilots who were given modafinil (200 mg at 2300, 0300, and 0700) during a 40-hour period of continuous wakefulness (Caldwell et al., 2000). In this helicopter study, modafinil significantly attenuated the effects of fatigue on the majority of flight maneuvers. The present F-117 investigation extends these earlier results by showing that beneficial modafinil effects also can be achieved with smaller 100 mg doses (administered at midnight, 0500, and 1000). In fact, the present findings, regarding the smaller dose, are in agreement with the results of a recently-published non-aviation study (Baranski et al., 2002) which showed that 100 mg doses, while not capable of sustaining performance at pre-deprivation levels, significantly attenuated the effects of fatigue.

The operational relevance of modafinil's beneficial effects on flight performance is clear, especially in light of the fact that untreated pilot fatigue is thought to be at least partially responsible for almost 8 percent of the Air Force's reportable Class A mishaps (personal communication, LtCol Thomas Luna, U.S. Air Force Safety Center, May, 2003). Although modafinil did not sustain flight performance at pre-deprivation levels, the fact that it significantly reduced fatigue-related flight-path deviations on the majority of maneuvers suggests it will attenuate the performance decrements associated with insufficient sleep during sustained and continuous aviation operations.

Modafinil side effects

As previously noted, prior to the present investigation there was one other aviator-performance study that examined the safety and efficacy of modafinil for sustaining the performance of sleep-deprived pilots. Although, in this earlier helicopter-pilot study

there were several positive modafinil effects, there also were a number of spontaneously-reported side effects which would be particularly problematic for pilots. Specifically, it was earlier observed that 600 mg modafinil (given in 3 divided 200-mg doses) often appeared to produce complaints of nausea, vertigo, and dizziness. At the time, it was unclear whether these effects were attributable to the dosage level, the testing situation, or some other unknown factor. However, since that time, researchers such as Buguet, Moroz, and Radomski (2003) and others have presented evidence suggesting that the dosage level was the likely culprit. Buguet, Moroz, and Radomski (2003) have shown that modafinil-related side effects of nausea and vomiting are dose dependent.

In light of these findings, and in an effort to reduce the possibility of unwanted side effects in the present investigation, a dosing strategy employing 100 mg doses rather than 200-mg doses of modafinil was chosen. Based on the results of the side-effects questionnaires that were administered at the conclusion of each testing session in this study, as well as the results of a simulator-sickness-questionnaire, the strategy was effective in that there were fewer overall complaints under the modafinil condition than under the placebo condition. The notable exception was that one participant complained of slight nausea only during the sleep-deprivation period in which he received modafinil. Although this subject attributed this to food intake and not the drug, it is always possible that modafinil was responsible for his nausea. However, none of the other pilots voiced similar complaints.

SUMMARY AND CONCLUSIONS

The present investigation on F-117 pilots indicated that modafinil (administered in 100-mg doses at midnight, 0500, and 1000) attenuated a number of the fatigue-related

effects associated with 37 hours of continuous wakefulness. Modafinil reduced the magnitude of tracking and attention errors on a multi-task cognitive battery. Modafinil attenuated fatigue-related increases in slow-wave EEG activity and mitigated the effects of sleep loss on oculomotor parameters (saccadic velocity and pupil diameter). Relative to the placebo/no-treatment condition, the drug improved self-perceptions of vigor, alertness, energy, and confidence, while decreasing feelings of depression and anger-hostility. However, subjective ratings of fatigue and sleepiness were not clearly affected by modafinil.

In terms of flight performance, modafinil produced beneficial effects on six of the eight flight maneuvers. Modafinil sustained control accuracy to within about 27 percent of baseline levels, whereas performance under the placebo/no-treatment condition degraded by an average of 82 percent.

The most pronounced performance benefits of modafinil administration were observed at the times during which the pilots had been awake for 24 to 32 hours, but there were positive effects at other times as well. Some of the self-reported mood and physiological-alertness benefits occurred as early as after 20 hours of continuous wakefulness.

The dosing scheme used in this study did not produce consistent evidence of any side effects which would contraindicate the administration of modafinil in actual flight operations. Despite one participant's complaints of mild stomach discomfort during his modafinil condition, there was no evidence that the 100-mg doses used here produced the frequent nausea and vertigo problems that earlier were associated with repeated 200-mg doses of modafinil in a helicopter-pilot study.

A general cautionary note about modafinil is that, unlike amphetamine, its beneficial effects are often not readily apparent to the fatigued individual. In fact, in the present study, most of the participants were unable to guess with any degree of certainty when they had received modafinil versus placebo. This observation, together with the apparent absence of robust drug effects on feelings of fatigue and sleepiness, needs to be considered in the operational environment. If pilots in real-world operations are unable to clearly "feel" the beneficial effects of modafinil, it is possible that they either will discontinue the drug (because they don't believe it is helping them) or they may inappropriately escalate the dose beyond safe levels in an effort to obtain a perceptible benefit. Therefore, it is essential that pilots be fully educated about modafinil's characteristic effects before this compound is used in operational settings.

In summary, modafinil should be considered a useful adjunct to the currently approved pharmacological fatigue countermeasure, dextroamphetamine. However, since at least at the dosage used here, 1) modafinil's efficacy is lower than what has been reported with amphetamine, and 2) modafinil's benefits are not as subjectively perceptible as those produced by the older compound, modafinil should not replace dextroamphetamine in the military's armament of fatigue countermeasures.

To further validate the utility of modafinil as an aviation fatigue remedy, modafinil next should be objectively evaluated in fighter pilots under actual in-flight conditions. Also, it is recommended that the present results (with 100 mg doses) be replicated in at least one additional flight-simulation study.

ACKNOWLEDGMENTS

The authors owe a debt of gratitude to all of those who made this exceptionally-demanding research possible. In particular, we thank the Commanding General, Brigadier General James P. Hunt; and the 49th Operations Group Commander, Colonel Andrew W. Papp for their unequivocal support. In addition, we deeply appreciate Major Richard Beavers for recruiting all of the volunteers, and we are very thankful for the fine cooperation from all of the personnel responsible for the operation of the Link F-117 Weapon System Trainer including Mr. Dean Wardell, Mr. Laurence Chaky, Mr. Rodrigo Duran, Mr. Jeffrey Glaze, Ms. Kellie Glaze, Mr. Kerry McClannahan, Mr. Brian Miller, Mr. Noel Terry, Mr. Robert Unger, and Mr. Dennis Whyman, as well as Mr. Adolf Wolfer of the Training System Squadron. We also owe a great deal to the F-117 instructor pilots Mr. James Brown, Mr. Richard Guidry, Mr. James Rials, Mr. Norman Schoening, and Mr. Jeffrey Ault for their invaluable assistance and guidance. Also, we deeply appreciate the efforts of Ms. Irene Rivas who coordinated the simulator availability times; and those of Lieutenant Colonel Gordon Peters, Captain Raymond Clydesdale, Captain Robert York, and Captain George Dockendorf, with the assistance of Technical Sergeant Bryan Cole, for providing full medical coverage. We very much appreciate the funding for this work that was provided by the Air Force Research Laboratory Human Effectiveness Directorate, the Air Force Office of Scientific Research, and the Oculomotor Steering Committee of the U.S. Army Medical Research and Materiel Command. In addition, we are thankful to Mr. Michael Nelson and Mr. Brian Johnson of Cephalon, Inc. for supplying the modafinil tablets and matching placebo tablets at no charge. We must acknowledge the invaluable behind-the-scenes support of

Major Brandon Doan, Chief of the Air Force Fatigue Countermeasures Branch. Without his help and support, this research would not have been possible. Finally, we are forever indebted to the F-117 pilots who sacrificed their time to serve as research participants on a project which has implications for aviation fatigue management throughout the world.

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